Functional Networks in Absolute Pitch and Auditory-Visual Synesthesia

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Abstract

The human brain is nowadays conceived of as a network controlling mind and behavior through a complex interplay of multiple brain areas. Whilst the brain networks' functionality has often been studied in average populations undergoing specific tasks, an equally informative approach is to draw inferences from exceptional populations with above-normal behavioral phenotypes. Such exceptional populations are constituted by subjects with absolute pitch (AP) or auditory-visual (AV) synesthesia. AP and AV synesthesia refer to a rare perceptual phenomenon where an auditory stimulus is accompanied by a concurrent conceptual category (a pitch label) or perception (a color), respectively. Both abilities are mostly found among musicians – a population which itself has attracted the interest of neuroscience as a model of neuroplasticity. The investigation of subjects with AP or AV synesthesia might thus be escpecially contributing to a better understanding of the human brain network. The current Ph. D. thesis comprises three studies in which electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) were used to asses functional networks in AP and AV synesthesia.

In Study I we analyzed EEG data from participants with and without AV synesthesia during resting-state (RS). AV synesthetes demonstrated increased parietal current density and increased top-down signal transmission from the superior parietal lobe to the left color processing area V4. Moreover, the AV specific functional network during RS was described by increased connectivity between auditory, parietal and visual brain areas.

In Study II we collected RS fMRI data from musicians with and without AP. A mass-univariate analysis revealed enhanced functional connectivity in middle frontal and parietal brain areas of AP musicians. By using multi-voxel pattern analysis, AP was successfully decoded from fine-grained connectivity patterns in the left auditory cortex.

In Study III we investigated effects of AP and musical proficiency on whole-brain functional connectivity. To this aim, EEG data from musicians with and without AP and non-musicians were collected during RS, music or audiobook listening. AP musicians displayed diminished whole-brain functional connectivity in comparison to non-musicians, whereas musicians without AP displayed an intermediate connectivity not fundamentally different from AP musicians or non-musicians. This group effect was only evident during auditory stimulation.

Study I and Study II coincide in showing that subjects with AP or AV synesthesia display enhanced connectivity within specific brain areas or distinct functional subnetworks. These connectivity increases might partially reflect altered cognitive or perceptual processes which are specific for the underlying phenomenon. Increased frontal connectivity in AP might relate to altered tonal working memory and/or associative memory mechanisms whereas increased signal transmission from parietal to visual areas in AV synesthesia may reflect top-down influences on concurrent color perceptions. The similarity between the two phenomena is emphasized by the involvement of the parietal lobe in both neural networks. Interestingly, the role of the parietal lobe in multimodal integration has been extensively discussed for AV synesthesia, but rarely for AP. We suggest that the parietal lobe unifies tones and pitch-labels to one holistic experience in AP, as it has been demonstrated for tones and colors in AV synesthesia. We further suggest that local connectivity increases during RS typify the AP musicians' and AV synesthetes' baseline from which neurophysiological processes start upon auditory perception. The finding of globally diminished connectivity during auditory perception in Study III extends the findings in Study II. Brain networks achieve high neural efficiency through high local clustering and few global long-range connections. The AP musicians' globally decreased connectivity during auditory perception could thus represent an example of neural efficiency when relevant cognitive functions are stimulated.

Zusammenfassung

Das menschliche Gehirn wird heutzutage als Netzwerk wahrgenommen, welches Geist und Verhalten durch ein komplexes Zusammenspiel von Gehirnarealen steuert. Die Funktionsweise des Hirnnetzwerks wurde häufig mithilfe experimenteller Aufgaben in durchschnittlichen Populationen untersucht. Ein ebenso informativer Ansatz besteht jedoch darin, Rückschlüsse aus der Untersuchung von aussergewöhnlichen Populationen zu ziehen. Beispiele für solche aussergewöhnlichen Populationen sind audio-visuelle Synästhetiker oder Menschen mit dem absoluten Gehör. Die Begriffe audio-visuelle Synästhesie und absolutes Gehör bezeichnen seltene Wahrnehmungsphänomene, bei welchen ein auditorischer Stimulus von einer zusätzlichen Farbwahrnehmung, respektive von einem konzeptuellen Tonnamen begleitet wird. Beide Phänomene treten gehäuft bei Musikern auf – eine Population welche ihrerseits das Interesse der Hirnforschung als ein Modell für Neuroplastizität geweckt hat. Die Erforschung von audio-visuellen Synästhetikern und absolut hörenden Musikern könnte deshalb besonders zum besseren Verständnis des menschlichen Hirnnetzwerks beitragen. Die vorliegende Dissertation beinhaltet drei Studien, welche die Funktionsweise des Hirnnetzwerks in audio-visuellen Synästhetikern und absolut hörenden Musikern mittels Elektroenzephalographie und funktioneller Magnetresonanztomographie untersuchen.

In Studie I werteten wir Elektroenzephalographiedaten von audio-visuellen Synästhetikern und Nicht-Synästhetikern im Ruhezustand aus. Dabei wiesen audio-visuelle Synästhetiker verstärkte parietale Stromdichten, sowie eine vermehrte Informationsübertragung vom superioren Parietallappen zum linken Farbareal V4 auf. Das funktionelle Hirnnetzwerk von audio-visuellen Synästhetikern war zudem durch verstärkte Konnektivitäten zwischen auditorischen, parietalen und visuellen Hirnarealen gekennzeichnet.

In Studie II verwendeten wir funktionelle Magnetresonanztomographie um absolut hörende Musiker und Musiker ohne absolutes Gehör im Ruhezustand zu untersuchen. Eine Massenunivariate Analyse ergab verstärkte funktionelle Konnektivitäten in frontalen und parietalen Hirnarealen von absolut hörenden Musikern. Ausserdem konnten absolut hörende Musiker von Musikern ohne absolutes Gehör anhand des Konnektivitätmusters im linken auditorischen Kortex unterschieden werden.

In Studie III untersuchten wir den Einfluss des absoluten Gehörs und des musikalischen Könnens auf die funktionelle Konnektivität des gesamten Gehirns, indem wir absolut hörende

Musiker, nicht absolut hörende Musiker und Nicht-Musiker während dem Hören von Musik oder Hörbüchern, sowie im Ruhezustand mittels Elektroenzephalographie untersuchten. Absolut hörende Musiker wiesen im Vergleich zu Nicht-Musikern global verminderte Konnektivitäten auf, während sich nicht absolut hörende Musiker nicht fundamental von den anderen Gruppen unterschieden. Dieser Gruppeneffekt konnte nur während dem Hören von Musik oder Hörbüchern festgestellt werden.

Studie I und Studie II zeigen übereinstimmend, dass audio-visuelle Synästhetiker und absolut hörende Musiker in spezifischen Hirnarealen oder Subnetzwerken verstärkte Konnektivitäten aufweisen. Dies mag teilweise auf kognitive oder perzeptuelle Prozesse zurückzuführen sein, die bezeichnend für das zugrunde liegende Phänomen sind. So könnten verstärkte frontale Konnektivitäten bei absolut hörenden Musikern auf veränderte Mechanismen im tonalen und/oder assoziativen Gedächtnis hinweisen, während eine vermehrte Informationsübertragung von parietalen zu visuellen Arealen bei audio-visuellen Synästhetikern auf veränderte Top-Down Einflüsse zurückzuführen sein könnte. Die Ähnlichkeit der beid en Phänomene wird durch die Beteiligung des Parietallappens in beiden neuronalen Netzwerken hervorgehoben. Interessanterweise wurde der Parietallappen im Bereich der audio-visuellen Synästhesie häufig mit multimodaler Integration in Verbindung gebracht, aber selten im Bereich des absoluten Gehörs. Wir vermuten, dass die holistische Wahrnehmung von einem Ton und dessen Bezeichnung bei absolut hörenden Musikern durch den Parietallappen zustande kommt, wie dieser auch bei audio-visuellen Synästhetikern Ton und Farbe zu einer einzelnen Wahrnehmung verbindet. Weiter schlagen wir vor, dass lokal verstärkte Konnektivitäten im Ruhezustand die neurophysiologische Grundlage für die weitere auditorische Verarbeitung bei audio-visuellen Synästhetikern und absolut hörenden Musikern bilden. Hirnnetzwerke erreichen eine effiziente Informationsübertragung durch starke lokale Konnektivitäten und wenige langreichende Verbindungen. Insofern könnten global verminderte Konnektivitäten bei absolut hörenden Musikern während auditorischer Verarbeitung in Studie III ein Beispiel für neuronale Effizienz darstellen wenn relevante kognitive Funktionen stimuliert werden.

Contents

CHAPTER 1

1 General Introduction

1.1 Absolute Pitch

Perfect or absolute pitch (AP) – the ability to identify and/or reproduce a musical pitch without the aid of an external reference (Takeuchi & Hulse, 1993) – is thought to occur in approximately 15 % of professional musicians (Baharloo, Johnston, Service, Gitschier, & Freimer, 1998). It is to be differentiated from relative pitch, a common ability in musicians, which refers to the identification of pitch by calculating the musical interval between two given tones. The causes for this fascinating phenomenon are still a matter of scientific debates. It seems that AP is not a consequence of enhanced long-term pitch memory representations since excellent long-term pitch memory is also a trait of untrained non-musicians: Most people will easily and accurately reproduce the pitches of well-known songs without any aid (Halpern, 1989). The increased familial aggregation (Baharloo, Service, Risch, Gitschier, & Freimer, 2000) and the linkage to the 8q24.21 chromosome (Theusch, Basu, & Gitschier, 2009) suggests, to some extent, the genetic predisposition of AP. However, the occurrence of AP is more frequent in cultures with tonal languages such as mandarin (Deutsch, Henthorn, Marvin, & Xu, 2006) and musical training is thought to encourage the formation of AP especially when commencing at an early age (Gregersen, Kowalsky, Kohn, & Marvin, 2001). As a unique opportunity to investigate genetic and environmental influences on human cognitive function (Zatorre, 2003), AP has thus raised the interest of cognitive neuroscience.

The investigation of AP is however a difficult task. Not only are subjects with AP rare, the scientific community additionally disagrees on regarding AP as an dichotomous or gradual ability. Based on the observation that pitch-naming performance in musicians usually varies across a broad range, some researchers have proposed the partitioning into multiple subgroups of AP musicians (Baharloo et al., 1998; Itoh, Suwazono, Arao, Miyazaki, &

Nakada, 2005). In that regard, pitch-naming performance is usually evaluated in tests where participants are required to correctly name a set of singly presented tones. However, the construction of such pitch-naming tests may explain at least some variation in pitch-naming performance. The choice of natural tones (e.g. piano tones) might for instance enhance the pitch-naming performance of musicians who are familiar with the instruments' timbre (Krumhansl & Iverson, 1992; Marvin & Brinkman, 2000). Further, not all musicians are familiar with the same tone frequency spectrum which is mostly defined by their choice of instrument - cellists or bassoonists are used to much lower tone frequencies than violinists or flutists. The range of frequencies in the pitch-naming test therefore constitutes another factor which might affect the musicians' pitch-naming performance. If tones are presented in fast succession, some participants might additionally profit from echoing tones to calculate a musical interval and thereby improve their pitch-naming performance. These issues have been addressed in some studies by the construction of pitch-naming tests using pure (synthesized sinusoidal) tones without a specific timbre across a broad frequency range and with Brownian noise between tones to prevent echoing tone tracks (Elmer, Rogenmoser, Kühnis, & Jäncke, 2015; Oechslin, Imfeld, Loenneker, Meyer, & Jäncke, 2010; Oechslin, Meyer, & Jäncke, 2010). Apart from test construction, virtually uncontrollable subject specific factors are likely to affect pitch-naming accuracy. For instance, anecdotal reports suggest that pitch perception may be shifted by a semitone in aged subjects with AP (W. D. Ward & Burns, 1982). Fatigue naturally varies within and between subjects, has tremendous effects on diverse cognitive functions (Lorist & Tops, 2003) and has been reported to shift pitch perception in a younger concert pianist with AP (Chaloupka, Mitchell, & Muirhead, 1994). Finally, pitch-naming accuracy is likely affected by the participants' motivation to perform in a pitch-naming test. Some studies included points for octave or semitone errors to account for subtle accuracy variations which on the other hand increases the chance to receive points by guessing (Dohn et al., 2013; Rogenmoser, Elmer, & Jäncke, 2015). We suggest that some variation in the pitch-naming performance of AP musicians is normal and presumably unavoidable. The dichotomous nature of AP is nonetheless suggested by a large-scale behavioral study with more than two thousand participants (Athos et al., 2007). In this Web-based study, participants were required to correctly name a total of 36 piano tones and 36 pure tones. Participants were given 1 point for correct answers and ¾ point for semitone errors (Figure 1).

Figure 1: Piano tone score as a function of pure tone score from more than two thousand participants. The area of circles is proportional to the frequency of scores. (Athos et al., 2007, fig. 1) https://www.pnas.org/content/pnas/104/37/14795/F1.large.jpg

Although pitch-naming performance varies across the whole range of possible scores in Figure 1, the frequency of scores clearly suggests two prominent groups: Subjects with AP and subjects without AP. Athos et al. (2007) propose a pure tone cut-off score of > 24.5 for AP musicians, based on a previous definition of their research group (Baharloo et al., 1998). This subdivision seems rather arbitrary given the many data points in close proximity of the cut-off line. It is however noteworthy that 77 % of the participants who claimed to have AP actually scored above this cutoff score. Thus, self-report might constitute a fairly accurate and non-arbitrary method to designate subjects with AP. Pitch-naming tests are nonetheless appropriate to assure that the frequency of pitch-naming scores in a sample of subjects with and without AP follows the bimodal distribution in Figure 1.

For the aforementioned reasons and in accordance with the majority of previous neuroscientific studies, AP was regarded as an dichotomous ability in Study II and III. The current neuroscientific knowledge of AP is described in more detail in the introductory parts of Study II and III. Briefly, it can be summarized as follows: AP ability is thought to arise from the interaction between auditory, frontal and parietal brain areas which have been related to pitch categorization, tonal working memory / associative memory and multimodal integration, respectively (Keenan, Thangaraj, Halpern, & Schlaug, 2001; Loui, Zamm, & Schlaug, 2012b; Luders, Gaser, Jäncke, & Schlaug, 2004; Schlaug, Jäncke, & Huang, 1995; Schulze, Gaab, & Schlaug, 2009; Wengenroth et al., 2013; Zatorre, Perry, Beckett, Westbury, & Evans, 1998). Although this network hypothesis is generally well accepted in the scientific community, most researches have investigated the function of a given brain area independent of other brain areas. The interdependency of brain areas is respected in investigations of functional connectivity which can be defined as the temporal correlation between spatially separated neurophysiological events (Friston, 1994). In Study II and Study III we therefore aimed at characterizing the AP specific network by means of functional connectivity.

1.2 Synesthesia

The umbrella term synesthesia refers to a rare perceptual phenomenon where a cognitive or sensory stimulus is accompanied by an additional sensory sensation (Cytowic, 2002) and is thought to occur in approximately 4.4 % of the general population (Simner et al., 2006). The scientific community suggests up to 80 different synesthesia types which are named and differentiated by their inducer-concurrent pair (Day, 2019). *Inducer* refers to the stimulus eliciting the synesthetic experience whereas the synesthetic experience itself is referred to as the *concurrent*. For instance, a tone elicits the perception of a color in tone-color synesthesia which is often listed under the more general term auditory-visual (AV) synesthesia to include synesthetes who perceive color upon other auditory stimuli such as noise or complex melodies. Synesthesia has to be differentiated from hallucinations and illusions which can be described as perceiving a concurrent perception without an inducing stimulus or as the altered perception of an inducing stimulus, respectively (World Health Organization, 2018). In contrast to hallucinations and illusions, synesthetic experiences generally do not interfere with normal daily functioning and seem to be unrelated to neurological or psychiatric disorders (Rich, Bradshaw, & Mattingley, 2005), despite a case report of a link to migraine (Alstadhaug & Benjaminsen, 2010).

Also, synesthesia has to be differentiated from the human brains' general preference to make non-arbitrary associations, as it is demonstrated by the Bouba/Kiki effect (Figure 2).

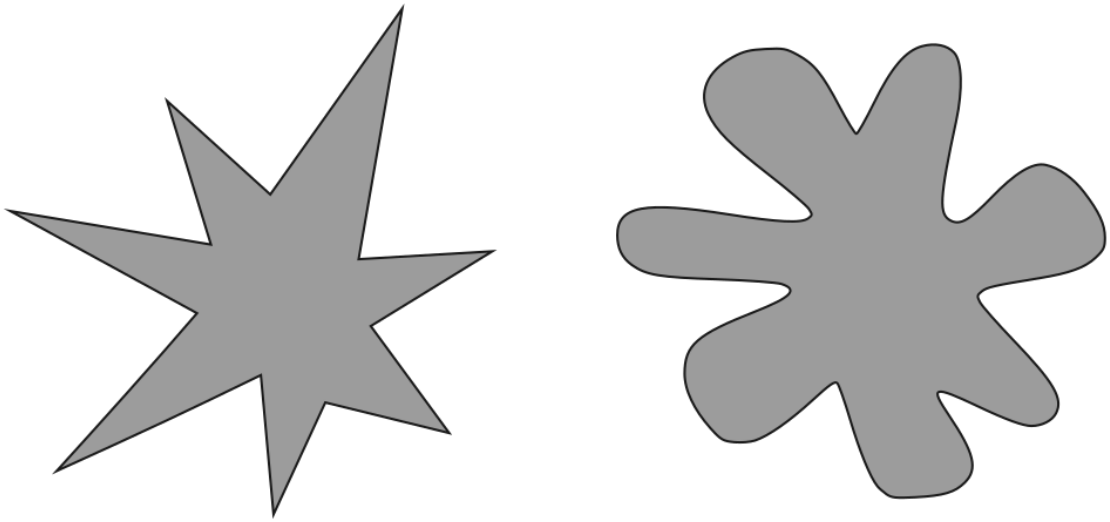

Figure 2: Demonstration of the Bouba/Kiki effect. Most people will refer to the left shape as "kiki" and to the right shape as "bouba". (Ramachandran & Hubbard, 2001b, fig. 7); Retrieved from https://commons.wikimedia.org/wiki/File:Booba-Kiki.svg

First described in 1929, a later experiment has shown that 95% of undergraduate students refer to the jagged shape in Figure 2 as "kiki" and to the curvy shape as "bouba" when asked to label these shapes with those two names, suggesting a non-arbitrary and interindividually consistent association between speech sounds and the visual shape of objects (Köhler, 1929; Ramachandran & Hubbard, 2001b). However, in contrast to everyday associations, synesthetic experiences are thought to be involuntary and highly automatic and synesthetes usually indicate to perceive inducer-concurrent pairs as an unitary whole, inseparable from each other (J. Ward, 2013).

The notion of involuntary, highly automatic and inseparable synesthetic experiences is supported by Stroop experiments with different types of synesthetes. Stroop experiments conflict the automatic activation of internal processes with a task which usually leads to decreases ind performance. In the classical Stroop task, participants were required to name the color of words. These words depicted color names that were either congruent (e.g. the word "red" printed in red) or incongruent (e.g. the word "blue" printed in red) with the color in

which the word was printed. Thus, in incongruent conditions, the automatic reading of words was conflicted by the task to name colors which lead to more mistakes and longer naming times than in congruent conditions (Stroop, 1935). This classical Stroop task has been adapted for the investigation of a grapheme-color synesthete who experienced colors upon the perception of written numbers (Mills, Boteler, & Oliver, 1999). In this experiment the synesthete was required to name the printed color of numbers that was either congruent or incongruent with the concurrent color perception. As expected, the authors found increased color naming times in incongruent conditions, demonstrating the automaticity and irrepressibly of synesthetic experiences. This synesthetic Stroop effect was later replicated for auditory-gustatory and AV synesthesia (Beeli, Esslen, & Jäncke, 2005; J. Ward, Huckstep, & Tsakanikos, 2006).

Another key characteristic of synesthesia is the consistency of concurrent experiences over time (J. Ward, 2013). It has been demonstrated that synesthetes are around 80% to 100% consistent when asked, without warning, to describe their concurrent color sensation three months after they had indicated concurrent colors for the same set of inducing stimuli (Mattingley, Rich, Yelland, & Bradshaw, 2001). Since the consistency of synesthetic experiences is more easily assessed than their automaticity, most researchers nowadays rely on test-retest consistency tests to designate synesthetes. The most frequently used consistency test battery for multiple types of synesthesia was provided by (Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007), which was also used in the present Ph. D. thesis (see Study I for a detailed description of the test). This test battery bears the advantage of providing an objective quantification with a cut-off score for synesthesia and has been validated in a large sample of almost three thousand participants (Carmichael, Down, Shillcock, Eagleman, & Simner, 2015). It thus constituted a unifying tool to designate synesthetes for neuroscientific studies of the last decade (Jäncke & Langer, 2011; Jäncke, Rogenmoser, Meyer, & Elmer, 2012; Zamm, Schlaug, Eagleman, & Loui, 2013).

The neuronal mechanisms of synesthesia are still under debate and are explained in more detail in Study I. Simplified, neuronal models of synesthesia can be differentiated by the proposed route of cross-activation (direct or indirect) between inducer and concurrent processing areas and by the proposed nature of the underlying difference in synesthetes (functional or structural), as it has been suggested by (Bargary & Mitchell, 2008). Figure 3

Figure 3: Differentiation of neural models of synesthsia by the proposed route of cross-activation (direct or indirect) between inducer and concurrent processing areas and by the the proposed nature of the underlying difference in synesthetes (functional or structural). Yellow fields denote active areas and blue fields denote inactive areas. (Bargary & Mitchell, 2008, fig. 2) https://www.semanticscholar.org/paper/Synaesthesia-and-cortical-connectivity-Bargary-Mitchell/5ac872d7abc1fa583159de610c67380c0041c78a/figure/1

Based on the observation of contextual influences on concurrent perceptions (Dixon, Smilek, Duffy, Zanna, & Merikle, 2003; Myles, Dixon, Smilek, & Merikle, 2003), most researchers have acknowledged the involvement of higher order brain areas in synesthesia (Grossenbacher & Lovelace, 2001; Hubbard, Brang, & Ramachandran, 2011). Also, most studiy results point towards functional rather than structural alterations in AV synesthesia (Jäncke & Langer, 2011; Neufeld, Sinke, Dillo, et al., 2012; Neufeld, Sinke, Zedler, et al., 2012). The hypothesis of increased functional connectivity between inducer, concurrent and higher order brain areas of AV synesthetes has been tested in Study I by an evaluation of whole-brain functional connectivity. Since it has been suggested that different subtypes of synesthetes employ a different directionality of communication between these areas (van Leeuwen, den Ouden, & Hagoort, 2011), we additionally included an evaluation of effective connectivity.

CHAPTER 2

2 Empirical Part Study I

Brauchli, C., Elmer, S., Rogenmoser, L., Burkhard, A., & Jäncke, L. (2018). Top-down signal transmission and global hyperconnectivity in auditory-visual synesthesia: Evidence from a functional EEG resting-state study. *Human Brain Mapping*, 39(1), 522–531.

2.1 Abstract

Auditory-visual (AV) synesthesia is a rare phenomenon in which an auditory stimulus induces a “concurrent” color sensation. Current neurophysiological models of synesthesia mainly hypothesize “hyperconnected” and “hyperactivated” brains, but differ in the directionality of signal transmission. The two-stage model proposes bottom-up signal transmission from inducer- to concurrent- to higher-order brain areas, whereas the disinhibited feedback model postulates top-down signal transmission from inducer- to higher-order- to concurrent brain areas. To test the different models of synesthesia, we estimated local current density, directed and undirected connectivity patterns in the intracranial space during two minutes of resting-state (RS) EEG in 11 AV synesthetes and 11 non-synesthetes. AV synesthetes demonstrated increased parietal theta, alpha and lower beta current density compared to non-synesthetes. Further, AV synesthetes were characterized by increased top-down signal transmission from the superior parietal lobe to the left color processing area V4 in the upper beta frequency band. Analyses of undirected connectivity revealed a global, synesthesia-specific hyperconnectivity in the alpha frequency band.

The involvement of the superior parietal lobe even during rest is a strong indicator for its key role in AV synesthesia. By demonstrating top-down signal transmission in AV synesthetes, we

provide direct support for the disinhibited feedback model of synesthesia. Finally, we suggest that synesthesia is a consequence of global hyperconnectivity.

2.2 Introduction

Synesthesia is a rare perceptual phenomenon where a sensory or cognitive stimulus (inducer) elicits a concurrent sensory sensation (Cytowic, 2002). In the case of auditory-visual (AV) and grapheme-color (GC) synesthesia a concurrent color perception (e.g. indigo blue) is triggered by an auditory stimulus (e.g. a “F sharp”) or a grapheme (e.g. a “B”), respectively. In the domain of GC synesthesia, two distinct types of synesthetic color sensations can be differentiated, namely those that are experienced in the external space (projectors) or experienced “in the mind’s eye” (associators) (Dixon, Smilek, & Merikle, 2004). While this terminology is reserved for GC synesthesia, the literature on AV synesthesia more likely discriminated between internally and externally experiencing synesthetes(Goller, Otten, & Ward, 2009; Jäncke, Rogenmoser, et al., 2012). Regarding the heterogeneity of synesthesia, manifold neurophysiological models have been suggested. The cross-activation model (Hubbard, Arman, Ramachandran, & Boynton, 2005; Ramachandran & Hubbard, 2001a) was inspired by the fact that the grapheme processing visual word form area (VWFA) lies adjacent to the color processing area V4 (Wade, Brewer, Rieger, & Wandell, 2002). Thus, synesthetic color sensations in GC synesthesia are thought to arise from direct cross-activation of the concurrent area (V4) by the inducer area (VWFA) due to a lack of pruning of structural connections between the areas during development. This perspective is supported by structural magnetic resonance imaging (sMRI) studies showing increased structural connectivity in the inferior temporal cortex (Rouw & Scholte, 2007) or demonstrating increased grey matter volumes in the vicinity of V4 (Jäncke, Beeli, Eulig, & Hänggi, 2009; Weiss & Fink, 2009). Also, using functional MRI (fMRI) greater V4 activity in response to graphemes versus non-graphemes in GC synesthetes compared to non-synesthetes was demonstrated (Hubbard et al., 2005).

The cross-activation model has been extended to a two-stage model (Hubbard, 2007; Hubbard & Ramachandran, 2005). In addition to cross-activation it proposes the binding of inducing and concurrent sensations by a parietal higher-order area. The parietal cortex is known to be involved in perceptual binding mechanisms (Robertson, 2003) and inhibition of this area has

been shown to attenuate synesthetic experiences (Esterman, Verstynen, Ivry, & Robertson, 2006).

A competing disinhibited feedback model (Grossenbacher & Lovelace, 2001) states that higher-order areas (e.g. the parietal cortex) serve as a multisensory nexus. Neuronal signals emerging from lower sensory areas are thought to propagate in a progressively converging manner through hierarchically organized modules until they reach this multisensory nexus. In synesthetes, feedback connections from the multisensory nexus to lower sensory areas are thought to be disinhibited. Consequently, the concurrent area V4 is activated by neuronal signals propagating backwards to lower sensory areas, which in turn leads to synesthetic color perceptions. This is supported by an fMRI study reporting increased functional connectivity in GC synesthetes between parietal and primary / secondary visual areas (Sinke et al., 2012). Also, hallucinogenic drugs were found to induce synesthetic experiences in non-synesthetes (Grossenbacher, 1997) implying that such experiences are reliant on typically existing adult networks rather than on additional structural connections between inducer and concurrent areas. In addition to these models, it has been argued that synesthesia might be a consequence of a globally altered brain network connectivity (Bargary & Mitchell, 2008). Global hyperconnectivity in GC synesthesia was found in a surface-based morphometry study (Hänggi et al., 2011), consistent with an fMRI resting state (RS) study showing a global increase of intrinsic inter-network connectivity (Dovern et al., 2012).

Knowledge about the neurophysiological processes in AV synesthesia is relatively sparse due to the small number of accessible subjects. Yet, parietal involvement in AV synesthesia has been demonstrated in multiple functional studies using fMRI (Neufeld, Sinke, Dillo, et al., 2012; Neufeld, Sinke, Zedler, et al., 2012) or electroencephalography (EEG) (Jäncke & Langer, 2011). Moreover, the parietal lobe has turned out to be strongly interconnected to other brain regions, even during RS (Jäncke & Langer, 2011). We thus argue that synesthetic color perceptions in AV synesthetes do not solely arise from direct cross-activation, but that additional parietal mechanisms play a pivotal role for this kind of synesthesia. Parietal involvement has been interpreted in favor of the two-stage model (Jäncke & Langer, 2011) but also in favor of the disinhibited feedback model (Neufeld, Sinke, Zedler, et al., 2012). These two models can be discriminated according to the proposed directionality of signal transmission. In fact, the two-stage model suggests bottom-up signal transmission from

inducer- to concurrent- to higher-order areas, whereas the disinhibited feedback model proposes top-down signal transmission from inducer- to higher-order- to concurrent areas. The correlational nature of the aforementioned studies renders it impossible to draw conclusions about the directionality of signal transmission in AV synesthesia (i.e., bottom-up vs. top-down). Therefore, studies investigating directed connectivity patterns are needed to directly test the assumptions made by the different neurophysiological models of synesthesia. So far, only one fMRI study using dynamic causal modeling has explored directed connectivity patterns in synesthesia (van Leeuwen et al., 2011). As a main result, the authors found that GC associators rely on top-down signal transmission while GC projectors are more likely characterized by bottom-up signal transmission. Directed connectivity patterns in AV synesthesia have not yet been investigated. Accordingly, in the present EEG study we evaluate directed connectivity in AV synesthetes. Further, only one study has evaluated undirected connectivity patterns in AV synesthesia on a global scale and found a generally altered brain network hyperconnectivity (Jäncke & Langer, 2011). In our analyses, we hence include a broad evaluation of undirected connectivity patterns. We used a sequential EEG procedure consisting of 1) estimating intracranial current-densities, 2) performing analyses of directed connectivity patterns between a priori defined inducer-, concurrent- and higher-order areas, and of 3) performing analyses of undirected connectivity patterns between globally distributed brain regions.

2.3 Methods

2.3.1 Participants

The analyses in this paper are based on RS data collected in the context of a previous mismatch negativity experiment (Jäncke, Rogenmoser, et al., 2012). In the present study, we evaluated the data of 11 AV synesthetes (mean age 30.7 ± 7.5, 9 female) who exclusively experienced colors in response to auditory non-linguistic stimuli and 11 non-synesthetes (mean age 29.6 ± 8.1, 9 female). Eight out of 11 AV synesthetes specified that they experience colors internally and only two externally. One synesthete could not explicitly attribute color sensation to the internal or external space. Furthermore, all participants were consistently right-handed with the exception of one ambidextrous person per group, as was revealed by the Edinburgh Handedness Inventory (Oldfield, 1971). The R statistics package (https://www.r-project.org/) was used to test for putative group differences in terms of cognitive capabilities

(Lehrl, Triebig, & Fischer, 1995) and musicianship (Gordon, 1989). All subjects denied taking medication or drugs, had no past or present neurological or psychiatric diseases, and revealed an unremarkable audiological status (Home Audiometer software, http://www.esseraudio.com/de/home-audiometer-hoertest.html). The subjects were paid for participation and gave written informed consent. The study was approved by the local ethics committee (Zurich) according to the Helsinki Declaration.

2.3.2 Test of genuineness synesthesia

All subjects performed a test of genuineness synesthesia (Eagleman et al., 2007). In this color-consistency test, subjects are required to choose the color from a color palette of 16.7 million different colors that most closely matches their synesthetic experience in response to randomly presented piano tones (13 tones, each of them presented three times, f0 frequency range from 261 to 523 Hz). The induced color sensations were coded by red-green-blue vectors in the range of 0-255. The consistency score for a specific piano tone was mathematically derived from the vector distance between the three randomly presented items. Following from this, the consistency score for each single subject was determined using the averaged tone consistency scores across the 13 piano tones. This test is widely used in synesthesia research (Jäncke & Langer, 2011; Jäncke, Rogenmoser, et al., 2012; Zamm et al., 2013) and has previously been shown to be sensitive for distinguishing between synesthetes and non-synesthetes (Eagleman et al., 2007).

2.3.3 EEG recording, experimental procedure, and data processing

Two minutes of eyes-closed RS EEG was recorded using a 32-channel montage according to the 10-20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP9, TP7, CP3, CPz, CP4, TP8, TP10, P7, P3, Pz, P4, P8, O1, Oz, and O2) with two additional eye channels (BrainAmp System, Germany). The data were collected with a sampling rate of 1000 Hz and a band-pass filter of 0.1-100 Hz. The nose was chosen as an online reference, and the electrode impedance was kept below 10 kΩ by using electro gel. The participants sat comfortably in a chair in a dimly lit sound-shielded Faraday cage and were told that EEG recording would be done while they rested with their eyes closed. The EEG data were processed using the Brain Vision Analyzer software (Version 2.0, Brainproducts, Germany). In particular, the data were filtered by employing infinite impulse response filters

(IIR; Butterworth; 48 dB/oct) with a high- and low-pass criteria of 0.5 and 40 Hz as well as a band-rejection filter of 50 Hz. Eye movement artefacts (i.e., blinks and saccades) were removed by using an independent component analysis (ICA) (Jung et al., 2000). The eye channels were discarded after ICA correction and the continuous artifact-free data were exported for further analyses with the sLORETA toolbox (Version 20160611; http://www.uzh.ch/keyinst/loreta.htm, (Pascual-Marqui, 2002)). Finally, in order to analyze directed connectivity the data was additionally down-sampled to 256 Hz (Pascual-Marqui, Biscay, Bosch-Bayard, et al., 2014).

2.3.4 Source estimation

To verify the source estimation of sLORETA, we reanalyzed the standard tone A (f0 = 440 Hz) of a mismatch negativity experiment previously performed with the same subjects (Jäncke, Rogenmoser, et al., 2012). The grand average was calculated as the average of all single subject event related potentials evoked by the standard tone A. Considering the whole-brain volume, maximal current density for the peak of the first negative deflection of the grand average at 115 ms after stimulus onset was estimated in the primary auditory cortex (-45, -30, 15; Montreal Neurological Institute, MNI). We are thus confident that source localization with the sLORETA toolbox works reasonably well.

2.3.5 Current Density Analyses

Current density during RS EEG was estimated for four frequency bands of interest, namely theta (4–7 Hz), alpha (8–12 Hz), lower beta (13–21 Hz), and upper beta (22–30 Hz). We specifically evaluated low- and high-frequency bands as both have been associated with multimodal integration (Kayser & Logothetis, 2009; Von Stein & Sarnthein, 2000), a key feature in AV synesthesia. The R statistics package was used for region-wise comparisons of current density between AV synesthetes and nonsynesthetes. We defined six regions of interest (ROI) according to current models of synesthesia postulating inducer-, concurrent-, and higher-order areas (Grossenbacher & Lovelace, 2001; Hubbard, 2007; Hubbard & Ramachandran, 2005). The ROIs consisted of single voxels and were located in the left and right primary auditory cortex (inducer areas), the left and right color processing area V4 and the primary visual cortex (concurrent areas) and the superior parietal lobe (higher order area). They are listed in Table I together with the ROIs for the analyses of undirected connectivity.

The Juelich Histological and the Harvard–Oxford cortical atlases (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; implemented in fMRIB software library: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) were used for a more detailed specification of brain regions. The ROIs for the left and right V4 were derived from an fMRI study performed with AV synesthetes (Neufeld, Sinke, Zedler, et al., 2012). Based on previous work (Esterman et al., 2006; Jäncke & Langer, 2011; Neufeld, Sinke, Dillo, et al., 2012) and to increase the power of our analysis, we selected a single medial ROI in the superior parietal lobe showing the highest mean current density across all subjects. All other ROIs consisted of a single centroid voxel of the respective Brodmann areas (BA). sLORETA source estimation is based on the smoothest solution of the inverse problem as the most plausible one (Pascual-Marqui, 2002). Centroid voxels of BAs are thus highly representative for the overall activity in the corresponding BAs and were also used in other studies of our research group(Elmer et al., 2015; Jäncke & Langer, 2011; Klein, Liem, Hänggi, Elmer, & Jäncke, 2016).

Table I Specification of ROIs Study I

BA	MNI coordinates (x, y, z)	Brain structure
BA5 L[b]	(-15, -45, 60)	SPL
BA5 R[b]	(15, -45, 60)	SPL
BA7 L[b]	(-20, -65, 50)	SPL
BA7 R[b]	(15, -65, 50)	SPL
BA39 L[b]	(-45, -65, 25)	IPL
BA39 R[b]	(45, -65, 25)	IPL
BA40L[b]	(-50, -40, 40)	aIPS
BA40R[b]	(50, -45, 45)	aIPS
BA19 L[a, b]	(-30, -70, -15)	VC V4
BA19 R[a, b]	(35, -80, -20)	VC V4
BA41 L[a, b]	(-45, -30, 10)	A1
BA41 R[a, b]	(45, -30, 10)	A1
BA44 L[b]	(-50, 10, 15)	Broca's area
BA44 R[b]	(55, 10, 15)	Broca's area
BA20 L[b]	(-45, -20, -30)	ITG
BA20 R[b]	(45, -20, -30)	ITG
BA21 L[b]	(-60, -20, -15)	MTG
BA21 R[b]	(60, -15, -15)	MTG
BA6 L[b]	(-30, -5, 55)	PreCG
BA6 R[b]	(30, -5, 55)	PreCG
BA8 L[b]	(-20, 30, 50)	SFG
BA8 R[b]	(20, 25, 50)	SFG
BA46 L[b]	(-45, 35, 20)	MFG
BA46 R[b]	(45, 35, 20)	MFG
BA9 L[b]	(-30, 30, 35)	MFG
BA9 R[b]	(30, 30, 35)	MFG
BA11 L[b]	(-20, 40, -15)	FP
BA11 R[b]	(20, 45, -20)	FP
BA17 M[a, b]	(0, -90, 0)	VC V1
BA7 M[a]	(0, -65, 50)	SPL

Superior parietal lobule, SPL; inferior parietal lobule, IPL; anterior intra-parietal sulcus, aIPS; visual cortex V4, VC V4; primary auditory cortex, A1; inferior temporal gyrus, ITG; middle temporal gyrus, MTG; precentral gyrus, PreCG; superior frontal

gyrus, SFG; middle frontal gyrus, MFG; frontal pole, FP; visual cortex V1, VC V1.
[a] Used for the analyses of current density and directed connectivity
[b] Used for the analyses of undirected connectivity

2.3.6 Directed Connectivity Analyses

RS EEG data were evaluated in four frequency bands(theta, alpha, lower beta, and upper beta) by using the R statistics package. Directed connectivity was computed between the six a-priori defined ROIs that were also used for group comparisons of current density (Table I). Directed connectivity was measured as isolated effective Coherence (iCoh) (Pascual-Marqui, Biscay, Bosch-Bayard, et al., 2014; Pascual-Marqui, Biscay, Bosch-bayard, et al., 2014). The iCoh is an approach for a frequency domain measure for Granger-causality (Granger, 1969). It is related to the widely used partial directed coherence (PDC) (Baccala & Sameshima, 2001). The iCoh is defined within the framework of a multivariate autoregressive (MVAR) model. The MVAR model for a time series X(t) with p >= 2 is written as:

$$X(t) = \sum_{k=1}^{p} A(k)X(t-k) + \varepsilon(t) \qquad (1)$$

where p is the model order, A(k) are the autoregressive coefficients, E(t) is the noise vector, and t denotes the discrete time. The element (i, j) of the matrices A(k) quantifies the direct causal influence for j → i which corresponds to Granger causality. The normalization procedure in the PDC formula has been criticized as the causal interaction between sender ROI j and receiver ROI i is influenced by the number and strength of interactions between j and all other receiver ROIs (Schelter, Timmer, & Eichler, 2009). As a consequence, the PDC (falsely) decreases, if the number and strength of receiver ROI interactions with j is high, even if the relationship between j and i remains unchanged. The iCoh overcomes this pitfall of the PDC by severing all possible connections between j and receiver ROIs that are not of interest:

$$\kappa_{i \leftarrow j}(\omega) = \frac{[\mathbf{S}_\varepsilon]_{ii}^{-1} \left| \left[\breve{\mathbf{A}}(\omega) \right]_{ij} \right|^2}{[\mathbf{S}_\varepsilon]_{ii}^{-1} \left| \left[\breve{\mathbf{A}}(\omega) \right]_{ij} \right|^2 + [\mathbf{S}_\varepsilon]_{jj}^{-1} \left| \left[\breve{\mathbf{A}}(\omega) \right]_{jj} \right|^2} \qquad (2)$$

where A(x) is the discrete Fourier transform, x denotes discrete frequency, and SE is the noise covariance. Thus, the iCoh can be formulated as the answer to the following question: “Given a dynamic linear system characterized by its autoregressive parameters, what would the equation for the partial coherence be if all connections are severed, except for the single one of interest?” (Pascual-Marqui, Biscay, Bosch-Bayard, et al., 2014; Pascual-Marqui, Biscay, Bosch-bayard, et al., 2014). The iCoh takes values between 0 and 1, with a zero value implying no causality. It was further shown that the iCoh comes to very similar results as the PDC when causal interactions between ROIs are simple but that the strength of the interaction between j and i remains unaffected by the number and strength of receiver ROI interactions with j when interactions between ROIs are more complex (Pascual-Marqui, Biscay, Bosch-Bayard, et al., 2014; Pascual-Marqui, Biscay, Bosch-bayard, et al., 2014). The statistical procedure used for evaluating group differences was equivalent to a single threshold test (Nichols & Holmes, 2002). In short, the two-tailed t-statistic between groups was calculated separately for the number of ROIs (nROI), number of frequency bands (nFreq), and direction of causal influence (A → B, B → A). This procedure yielded in a matrix consisting of nROI * (nROI - 1) * nFreq = 120 statistical tests, serving as the test statistic “K”. Evaluation of between group differences was repeated after randomly switching the group labels for a total of M = 5000 random permutations. For each permutation, the maximal t-statistic was stored giving the permutation distribution for the maximal statistic. Finally, the FWE corrected p-values of single cells of K were estimated by counting the number of cases where the t-statistic of a random permutation was equal to or greater than the t-statistic of a single cell of K and by dividing this number by M. The BrainNet Viewer was used for the visualization of the results (https://www.nitrc.org/projects/bnv/ ; (Xia, Wang, & He, 2013)).

2.3.7 Undirected Connectivity Analyses

To investigate AV synesthesia on a global scale, we also evaluated undirected connectivity between 29 ROIs (Table I). The selected ROIs were chosen according to previous studies in AV synesthesia showing the involvement of primary and secondary auditory- (Beeli, Esslen, & Jäncke, 2008; Jäncke & Langer, 2011; Jäncke, Rogenmoser, et al., 2012); primary and secondary visual- (Beeli et al., 2008; Jäncke, Rogenmoser, et al., 2012; Neufeld, Sinke, Dillo, et al., 2012); parietal- (Jäncke & Langer, 2011; Neufeld, Sinke, Dillo, et al., 2012; Neufeld, Sinke, Zedler, et al., 2012); and frontal brain areas (Beeli et al., 2008; Dovern et al., 2012). As a consequence of sLORETAs smoothing parameter (Pascual-Marqui, 2002) and to guarantee that individual ROIs indeed reflected distinct functional areas, we set a minimum of 1.5 cm as inter-ROI distance. Undirected connectivity was computed on the cross-spectra between EEG epochs for distinct frequency bands. Accordingly, for every single subject, the 2 min of RS EEG were segmented into epochs of one second and undirected connectivity was computed in the following frequency- bands: theta, alpha, lower beta, and upper beta. The undirected connectivity between two ROIs X and Y for a particular frequency (x) was calculated as lagged phase synchronization (Pascual-Marqui, 2007) according to the following formula:

$$\varphi^2_{x \underset{\longrightarrow}{\longleftarrow} y}(\omega) = \frac{\left[\mathrm{Im}\left(s_{\breve{x}\breve{y}\omega}\right]^2\right.}{1 - \left[\mathrm{Re}\left(s_{\breve{x}\breve{y}\omega}\right]^2\right.} \qquad (3)$$

In this work, we concentrated on a lagged measurement for undirected connectivity between ROIs. This has the major benefit that it is comparable to our analysis of directed connectivity which is—by its nature—lagged. Phase synchronization is quantified as a value between 0 (no synchronization) and 1 (perfect synchronization) and is defined as “the absolute value of the complex valued (hermitian) coherency between the normalized Fourier transforms” (Pascual-Marqui, 2007). The term “lagged” refers to the process of removing the effect of zero-lag instantaneous interactions on phase synchronization which are contained in the real (Re) part of the Hermitian covariance (i.e., in the denominator of eq. (1)). The normalized Fourier transforms (Xjx) of the phase-information cross-spectra (SXYx) are defined as

$$\breve{X}_{j\omega} = \left(X^{*}_{j\omega} X_{j\omega}\right)^{-1/2} X_{j\omega} \qquad (4)$$

with j denoting the j-th EEG epoch. As an output of the analysis, we obtained 29 x 29 square matrices, separately for each single subject and predefined frequency band. ROIs indicate rows and columns, whereas a single element contains the mean lagged phase synchronization between two ROIs during 2 min of RS EEG. These matrices were then submitted to statistical analyses with network-based statistic (Zalesky, Fornito, & Bullmore, 2010).

2.3.7.1 Network-based statistic (NBS)

Between-group differences in undirected connectivity were statistically evaluated by using the network-based statistic (NBS) toolbox (Zalesky et al., 2010) separately for each frequency band (theta, alpha, lower beta, upper beta). NBS is based on a nonparametric supra-threshold cluster test which is often used in fMRI-analyses (Nichols & Holmes, 2002). A network or "graph component" is thus defined by "interconnectedness of suprathreshold links in topological space" (Zalesky et al., 2010). NBS controls the family-wise error (FWE) that arises in multiple testing by 1) computing the t-test statistic for each connection. Edges exceeding a specific threshold form a suprathreshold network. The size, i.e. the number of edges, of the largest observed suprathreshold network serves as the test statistic "k". 2) Run a total of M = 5000 permutations where for each permutation, the group labels of subjects are randomly switched and the size of the largest random suprathreshold network is stored. 3) The FWE corrected p-value of k is estimated by counting the total number of permutations where the size of the largest random suprathreshold is equal to or greater than k and by dividing this number by M. In our analyses, only suprathreshold networks exceeding a t-value of two (t = 2.2 for the alpha frequency band) were considered as functionally meaningful.

2.4 Results

2.4.1 Behavioral data

AV synesthetes and non-synesthetes did not differ significantly in age (t(20) = 0.326, p = .74), general cognitive capability (t(20) = 1.391, p = .18), nor in the tonal (t(20) = 1.173, p = .25) and rhythmical (t(20) =0.568, p=.57) part of the test for musical aptitudes (t-tests for independent samples, two tailed). The two groups differed significantly in consistency scores, with AV synesthetes demonstrating shorter color distances (i.e. a higher consistency) (mean = 0.82 ± 0.29) than non-synesthetes (mean = 1.95 ± 0.45) (t(20) = 7.064, p < .001; t-test for independent samples, two-tailed).

2.4.2 Current density

AV synesthetes showed increased current density compared to non-synesthetes in the parietal lobe: theta (t(13.46) = -2.15 , p = .050 , two-tailed Welch's test); alpha (t(14.86) = -2.26 , p = . 039 , two-tailed Welch's test) and lower beta (t(10.76) = -2.52 , p = .029 , two-tailed Welch's test) (uncorrected p-values). The two-tailed statistic also yielded a trend toward higher current density in the parietal lobe for the upper beta frequency band in AV synesthetes than in non-synesthetes: t(10.47) = -1.82 , p = .098 , two-tailed, uncorrected. Non-synesthetes did not demonstrate stronger current density than AV-synesthetes.

2.4.3 Directed connectivity

AV synesthetes demonstrated significantly increased directed connectivity in the upper beta frequency band from the superior parietal lobe (BA7) to the left color processing area V4 (mean iCoh = 0.188 ± 0.110) compared to non-synesthetes (mean iCoh = 0.044 ± 0.035 SD) (t(12.06) = -4.12, p = .048, FWE corrected). Compared to AV synesthetes, non-synesthetes did not reveal increased directed connectivity, irrespective of connection orfrequency band. Figure 4 displays the between-group differences in iCoh for the upper beta frequency band.

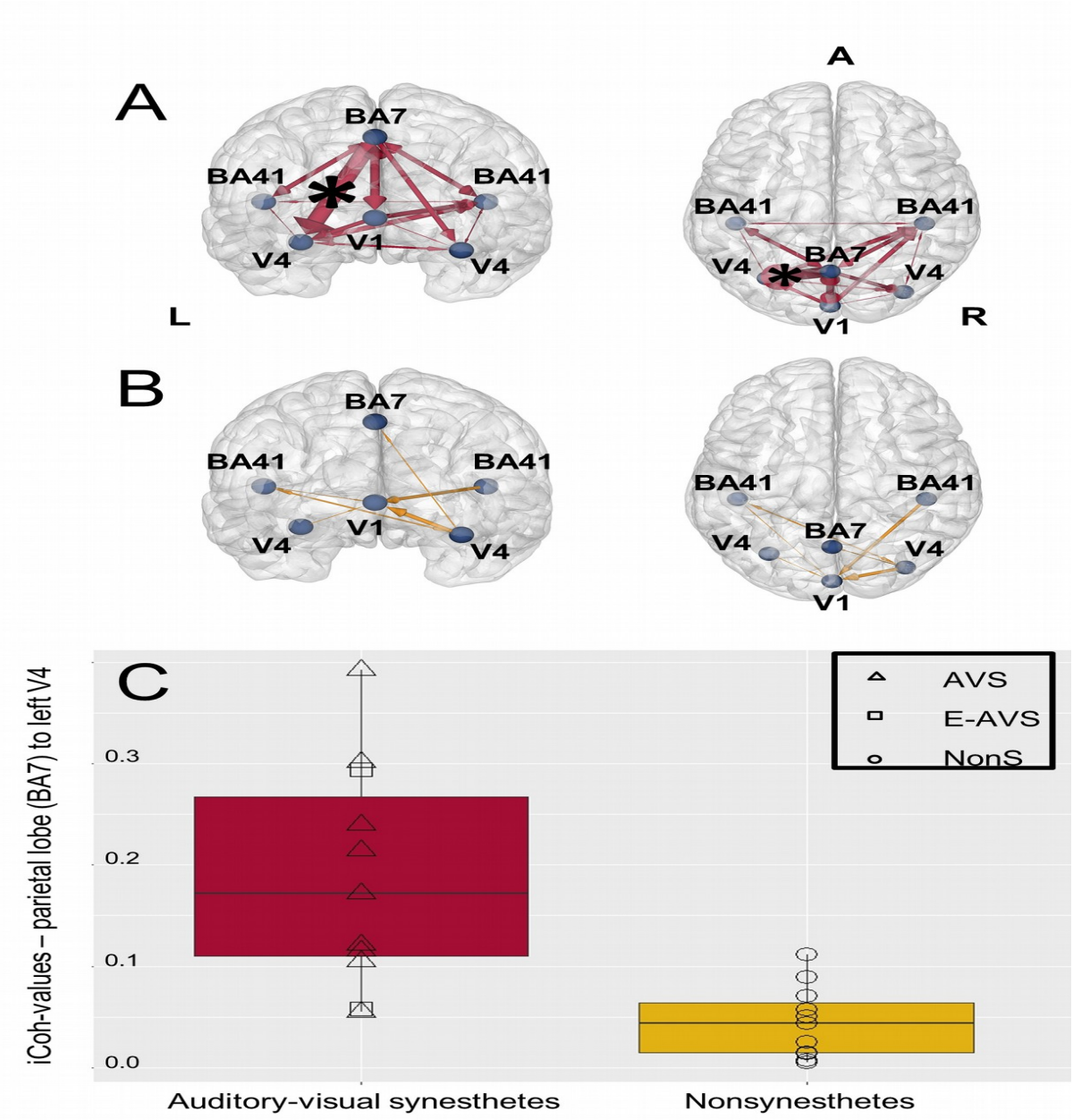

Figure 4: Directed connectivity differences between auditory-visual synesthetes (A) and nonsynesthetes (B), measured as isolated effective Coherence (iCoh) between parietal- (BA7), primary auditory (BA41), primary visual (V1), and secondary visual (V4) brain areas in the upper beta frequency band. Arrow thickness is weighted by absolute t values. (C) Directed

connectivity values from the parietal lobe to left color processing area V4 for auditory-visual synesthetes and nonsynesthetes (P<0.05, FWE corrected). A = anterior; L = left hemisphere; R = right hemisphere; AVS = auditory-visual synesthetes; E-AVS = auditory- visual synesthetes experiencing colors externally; Non = 5nonsy- nesthetes.

2.4.4 Undirected connectivity (NBS)

AV synesthetes showed increased undirected connectivity in the alpha (p = .042, FWE corrected) frequency band compared to non-synesthetes. The network in the alpha frequency band consisted of 20 nodes and 45 edges and was characterized by global intra- and interhemispheric connections between auditory, visual and parietal brain areas. The mean lagged phase synchronization of all edges of the alpha network was 0.168 (± 0.036) in AV synesthetes, and 0.086 (± 0.020) in non-synesthetes. The alpha network is displayed in Figure 5. We did not find significant group differences in the theta, lower beta or upper beta frequency bands. We also did not identify increased undirected connectivity in non-synesthetes compared to AV synesthetes.

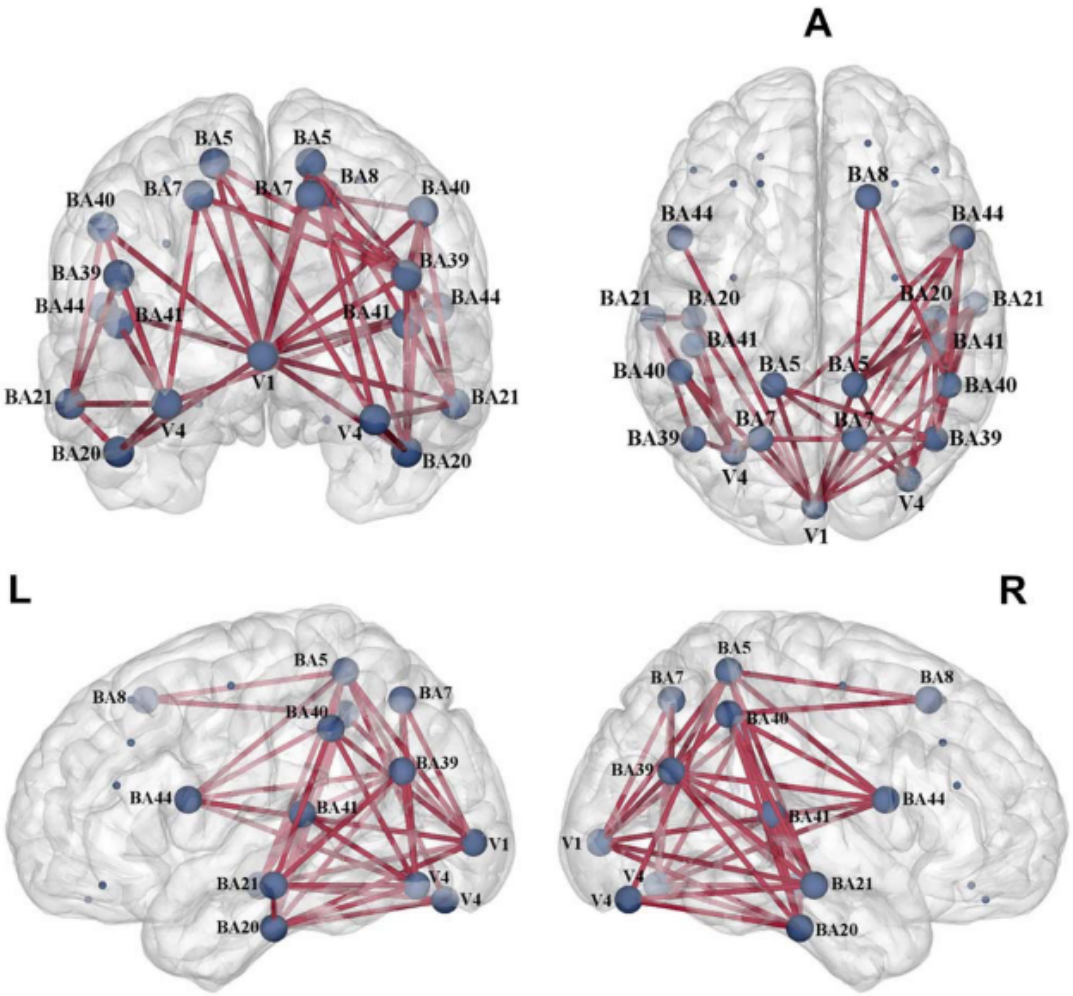

Figure 5: Statistical difference in the connectivity profile between auditory-visual synesthetes and nonsynesthetes in the alpha frequency band. Auditory-visual synesthetes showed significantly increased undirected connectivity (depicted in red) ($P < 0.05$, FWE corrected). A = anterior; L = left hemisphere; R = right hemisphere. Red lines = edges; blue dots = nodes.

2.5 Discussion

Current neurophysiological models of synesthesia mainly hypothesize hyperconnected and hyperactivated brains. Accordingly, it has previously been argued that synesthesia might be a consequence of a globally altered brain network connectivity (Bargary & Mitchell, 2008; Hänggi et al., 2011; Jäncke & Langer, 2011). The next section discusses our results in sequential order.

2.5.1 Parietal involvement

We found higher parietal current density in AV synesthetes compared to non-synesthetes in a broad frequency range. Although an uncorrected significance level ($p < .05$) was employed, our findings are in line with previous studies showing parietal involvement in AV synesthesia (Jäncke & Langer, 2011; Neufeld, Sinke, Dillo, et al., 2012; Neufeld, Sinke, Zedler, et al., 2012). In accordance with a previous EEG study (Jäncke & Langer, 2011), we demonstrated parietal involvement in AV synesthesia even during RS. We suggest that the parietal lobe plays a key role for this specific kind of synesthesia. Accordingly, we believe that direct cross-activation of V4 by inducer areas (Hubbard et al., 2005; Ramachandran & Hubbard, 2001a) is not a sufficient explanation for the neurophysiological basis of AV synesthesia.

2.5.2 Top-down signal transmission

We evaluated directed connectivity patterns to directly test the assumptions made by the two-stage and disinhibited feedback models. The analysis revealed that even during RS, AV synesthetes were characterized by increased top-down signal transmission from a higher-order area in the superior parietal lobe to the concurrent color processing area V4 in the upper beta frequency band. Interestingly, frequencies above 20 Hz have previously been associated with top-down signal transmission during an auditory-visual sensory integration paradigm in rhesus monkeys (Kayser & Logothetis, 2009). It could thus be that multimodal integration in AV synesthesia is driven by top-down signal transmission in higher frequencies.

An fMRI study performed with AV synesthetes reported stronger connectivity of the parietal cortex with primary auditory and primary visual areas (Neufeld, Sinke, Zedler, et al., 2012).

Although this finding is a strong argument for the disinhibited feedback model of synesthesia, the correlational nature of the aforementioned study renders it impossible to draw any conclusions about the directionality of signal transmission between brain areas. By contrast, our results provide direct support for the disinhibited feedback model in AV synesthesia which postulates top-down signal transmission from higher-order areas to concurrent processing areas. On the contrary, since we did not reveal increased directed connectivity in AV synesthetes from primary auditory areas to V4 or from V4 to the superior parietal lobe, our results do not provide evidence for a contribution of bottom-up signal transmission to AV synesthesia, as proposed by the two-stage model.

Different subtypes of synesthetes were found to rely on different signal transmission pathways (van Leeuwen et al., 2011). Using dynamic causal modeling, this study demonstrated top-down signal transmission in internally perceiving GC associators vs. bottom-up signal transmission in externally perceiving GC projectors. Since most of the AV synesthetes who participated in this study experience synesthetic colors internally, it is conceivable to assume that increased top-down signal transmission was primarily driven by the majority of internally perceiving subjects.

2.5.3 Global hyperconnectivity

The undirected connectivity analyses investigated between-group differences in brain networks on a global scale. This approach yielded stronger and globally extended connectivity patterns in AV synesthetes compared to non-synesthetes in the alpha frequency band. In particular, we revealed increased undirected connectivity between auditory, parietal and visual brain regions that have previously been shown to differ in a variety of phenotypes of synesthesia (Beeli et al., 2008; Esterman et al., 2006; Hubbard et al., 2005; Jäncke, Rogenmoser, et al., 2012). Long-range connectivity in the alpha frequency band was specifically associated with the processing of internal mental context, i.e. with top-down processing (Von Stein & Sarnthein, 2000). Therefore, it is plausible to assume that the global hyperconnectivity we revealed in the alpha frequency band might be an indicator for top-down processes in AV synesthesia. Notably, our results are in line with a previous RS EEG study investigating AV synesthetes and reporting globally distributed hubs with stronger interconnections in synesthetes compared to non-synesthetes (Jäncke & Langer, 2011).

Furthermore, an fMRI study targeting at evaluating undirected connectivity in AV synesthesia found stronger connectivity of the parietal cortex with primary auditory and primary visual areas (Neufeld, Sinke, Zedler, et al., 2012), which is also a prominent feature in our network of undirected connectivities. Yet, the authors used a seed-based approach which results in very large correlation matrices. Therefore, the connectivity of only a single or very few seed regions can be calculated. Here, we overcome this issue by calculating the undirected connectivity between 29 a-priori defined, literature-based and globally distributed nodes.

We find hyperconnected brains of AV synesthetes and suggest that synesthesia per se might be a consequence of global hyperconnectivity. This due to the fact that global hyperconnectivity has previously also been reported in GC synesthesia (Hänggi et al., 2011). Moreover, different forms of synesthesia are likely to co-occur (Novich, Cheng, & Eagleman, 2011). In our study, synesthetes were recruited by and exclusively tested on the occurrence of AV synesthesia. Although all AV synesthetes reported to experience colors only in response to auditory non-linguistic stimuli, we can not rule out the possible co-occurrence of other synesthesia forms in some synesthetes. Future studies could contribute to a more holistic understanding of the umbrella term ‘synesthesia’ by a more complete description of inducer-concurrent pairings.

2.6 Limitations

The small sample size of the present study did not allow for appropriate statistical analyses of subsamples. Whether different subtypes of AV synesthetes rely on different signal transmission pathways (bottom-up vs. top-down) remains a matter of research. Future studies should differentiate between subgroups of associator and projector synesthetes; respectively between internally and externally color experiencing synesthetes.

2.7 Conclusions

The functional involvement of the superior parietal lobe even during rest is a strong indicator for its key role in AV synesthesia. By demonstrating top-down signal transmission in AV synesthetes, we deliver direct support for the disinhibited feedback model of synesthesia. Finally, we suggest that synesthesia is one consequence of global hyperconnectivity.

CHAPTER 3

3 Empirical Part Study II

Brauchli, C., Leipold, S., & Jäncke, L. (2019). Univariate and multivariate analyses of functional networks in absolute pitch. *NeuroImage*, 189, 241–247.

3.1 Abstract

Absolute pitch (AP) refers to the rare ability to identify the pitch of any given tone without an external reference tone. Previous studies have shown that during auditory processing, AP musicians activate the auditory cortex (AC), the prefrontal cortex (PFC), and parietal areas of the brain. Therefore, it has been hypothesized that AP is sustained by a widespread functional network. In the present functional magnetic resonance imaging (fMRI) study, we tested this hypothesis by employing a mass-univariate analysis of resting-state functional connectivity within the AC, the PFC, and parietal areas in a large sample of musicians with and without AP (N=100). AP musicians showed increased functional connectivity in the left middle frontal gyrus (MFG), left intraparietal sulcus (IPS), and right superior parietal lobule (SPL). These results provide the first evidence for an AP-specific network characterized by increased functional connections in higher-order cognitive areas. Interestingly, AP was not associated with increases in functional connectivity of the AC, but AP was successfully decoded from functional connectivity patterns in the left AC using multi-voxel pattern analysis (MVPA), with group classification accuracy being highest for the left Heschl's gyrus (HG). MVPA can capture fine-grained patterns in the brain connectivity profile of AP musicians, whilst a mass-univariate analysis is sensitive to macroscopic trends in the data. The successful differentiation of AP musicians by MVPA but not by a mass-univariate analysis of connectivity in the AC thus indicates that AP musicians differ in the fine-grained rather than the macroscopic AC function. Based on our findings, and in light of current literature, we propose pitch-label associations, tonal working memory, pitch categorization, and multimodal

integration as potential mechanisms underlying the AP ability. This set of psychological functions is controlled by a distributed functional network and a particular AC connectivity pattern only present in AP musicians.

3.2 Introduction

Perfect or absolute pitch (AP) is defined as the ability to identify and/or reproduce a musical pitch without the aid of a reference pitch(Takeuchi & Hulse, 1993). AP is thought to originate from the interaction of genetic factors (Baharloo et al., 2000) and a highly intensive musical training beginning at an early age (Deutsch et al., 2006; Gregersen et al., 2001). As an opportunity to investigate the influence of genetic and environmental factors on neural and cognitive functions (Zatorre, 2003), AP has thus raised the interest of the neuroscientific community which, in turn, has had a substantial impact on the interpretation of the mechanisms underlying AP.

Zatorre (2003) suggested that AP musicians differ from musicians without AP in that they encode pitches within narrower categories, and the encoding of sound categories is associated with the activation of the auditory cortex (AC) (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005). The numerous reports of functional and structural alterations in the AC of AP musicians might thus relate to refined pitch categorization (Keenan et al., 2001; Luders et al., 2004; Ohnishi, 2001; Schlaug et al., 1995; Schulze et al., 2009; Wengenroth et al., 2013; Zatorre et al., 1998). Apart from the AC, higher-order areas (e.g., the intraparietal sulcus (IPS) and the prefrontal cortex (PFC)) involved in multimodal psychological processing are associated with AP. Schulze et al. (2009) showed that AP musicians display less activation in the right IPS than musicians without AP during a tonal working memory task. Since decreased cortical activation has been interpreted as a marker for neural efficiency (Haier et al., 1988; Neubauer & Fink, 2009), the decreased IPS activation observed in AP musicians might reflect their efficient use of tonal working memory mechanisms. On the other hand, Zatorre (1998) argued that AP musicians do not need to access tonal working memory at all due to the automatic retrieval of pitch-label associations. Such pitch-label associations are assumed to rely on the recruitment of the left PFC because it has been shown that the left PFC is activated during pitch labeling

(Wengenroth et al., 2013; Zatorre et al., 1998) and is involved in learning pitch-label associations in non-musicians (Bermudez & Zatorre, 2005).

Given the involvement of multiple brain areas and their broad functionality, a recent review stated that AP ability is subserved by a distributed network comprising several brain areas, including some outside of the AC (Hou, Chen, Song, Sun, & Beauchaine, 2016). To date, relatively few structural or functional connectivity studies investigating AP musicians have been conducted. Altered myelination and fractional anisotropy in the bilateral AC has been demonstrated in studies using diffusion tensor imaging (Kim & Knösche, 2016; Loui, Li, Hohmann, & Schlaug, 2011; Oechslin, Imfeld, et al., 2010). On the basis of cortical thickness covariations, Jäncke et al. (2012) identified enhanced bilateral peri-sylvian connectivity in AP musicians, though a connectivity decrease outside of the peri-sylvian region was observed.

Functional studies focussed on the evaluation of resting-state connectivity. Functional networks during resting-state have been shown to be robust and reliable (Damoiseaux et al., 2006; Shehzad et al., 2009), and therefore reflect functionally meaningful activity rather than noise (Biswal, Yetkin, Haughton, & Hyde, 1995). Moreover, resting-state functional connectivity is related to the structural brain organization (Greicius, Supekar, Menon, & Dougherty, 2009), describes distinct populations within the auditory domain (Jäncke & Langer, 2011; Klein et al., 2016) and brain activity prior to stimulus perception has been shown to be predictive of later behavioral performance (Otten, Quayle, Akram, Ditewig, & Rugg, 2006; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008). Resting-state functional connectivity in AP musicians might thus reflect the baseline from which neurophysiological processes start upon auditory perception (Gusnard & Raichle, 2001). Using electroencephalography, Elmer et al. (2015) reported increased resting-state functional connectivity between the left AC and the left PFC in AP musicians. Other research groups identified increased resting-state connectivity between the right planum polare and the left and right AC in AP musicians (Kim & Knösche, 2017). Also, a graph theoretical evaluation of resting-state connectivity revealed increased degrees, clustering, and local efficiency in the left AC of AP musicians (Loui et al., 2012b). Taken together, these functional connectivity studies might have been unable to capture the full extent of the AP-specific network, since connectivity was only calculated between a few predefined brain regions (Elmer et al., 2015;

Kim & Knösche, 2017). Notably, whole-cortex functional connectivity was only calculated in one of these studies (Loui et al., 2012b).

In the present study, we used functional magnetic resonance imaging (fMRI) to collect data from AP musicians and musicians without AP (Non-AP musicians). Non-AP musicians were chosen as a control group since they allow for the investigation of AP ability without the confounding effects of musicality or musical experience. Analogous to the aforementioned functional connectivity studies, AP and Non-AP musicians were recorded during resting-state. We tested the hypothesis that AP is sustained by a specific resting-state network by employing a mass-univariate analysis of voxel-wise connectivity measures considering *local* and *global* aspects of the whole-brain. These connectivity measures were calculated from smoothed fMRI data. Additionally, we used multi-voxel pattern analysis (MVPA) (Haxby et al., 2001; Norman, Polyn, Detre, & Haxby, 2006) of the same connectivity measures derived from unsmoothed fMRI data. Calculating connectivity from unsmoothed fMRI data conserve group informative spatial patterns that would be blurred by smoothing. Moreover, in contrast to mass-univariate analyses, MVPA is based on the detailed spatial patterns of connected voxels, which might be more informative for discrimination between AP and Non-AP musicians.

3.3 Methods

3.3.1 Participants

Previous studies in neuroscience have recently been criticized for often analyzing data from small samples, which not only reduces the chance of detecting a true effect, but also decreases the probability that a significant result reflects a true effect (Button et al., 2013). Consequently, we analyzed a relatively large sample comprising 50 AP and 50 Non-AP musicians. AP and Non-AP musicians were recruited from local conservatories and orchestras. All musicians were professionals, music students, or highly trained amateurs between 18 and 37 years old. Most of the musicians played the piano as the main instrument and played at least one additional instrument on a regular basis. The assignment of the musicians to the groups was based on self-report and can therefore not be attributed to an arbitrary cut-off. AP and Non-AP musicians were matched for age, sex, handedness, and cognitive capability (see Table II).

TABLE II. Group Demographics Study II

Measure	AP Mean (±SD)	Non-AP Mean (±SD)	*P*-value
Age (years)	26.14 (±4.88)	25.26 (±4.46)	.35
Sex ratio (female / all)	0.44 (-)	0.48 (-)	.84
Handedness ratio (right / (right + left + ambidextrous))	0.88 (-)	0.90 (-)	.56
Cognitive capability[a]	27.65 (±5.25)	29.10 (±4.72)	.15
AoC[b] (years)	6.00 (±2.36)	6.52 (±2.42)	.30
Training Effort[c] (hours played)	16304 (±12818)	13903 (±10072)	.30
AMMA total score[d]	66.24 (±6.19)	63.32 (±6.97)	.03
Pitch-naming score (percent correct)	77.54 (±19.37)	23.93 (±19.26)	< .001

[a]MWT-B total scores according to (Lehrl, 2005)
[b]Age of commencement of musical training
[c]Training effort measured as total of hours played during lifetime
[d]"Advanced Measures of Music Audiation" (AMMA) according to (Gordon, 1989)

AP and Non-AP musicians were also matched for their musical training in terms of age of commencement of musical training and the total of hours played during lifetime (training effort). Musical aptitude was quantified using the "Advanced Measures of Music Audiation" (AMMA) test (Gordon, 1989). In this test, participants need to decide whether 30 successive pairs of short piano melodies are equivalent, different with respect to tonality, or different with respect to rhythmicity. Pitch-naming ability was evaluated using an online adaptation of an in-house test (Oechslin, Meyer, et al., 2010). In this test, participants had to correctly name a total of 108 pure tones ranging from C3 to B5 (tuning: A4 = 440 Hz). Each tone was presented three times for 500 ms in a pseudo-randomized order, in which the same tone was

never presented successively. Tones were preceded and followed by 2 s of Brownian noise. Pitch-naming scores were calculated as the percentage of correctly named tones without counting octave errors.

3.3.2 fMRI data acquisition and procedure

Imaging data were acquired on a Philips Ingenia 3 T scanner (Philips Medical Systems, Best, The Netherlands). We obtained 210 volumes of resting-state functional images for each participant using a T2*-weighted gradient echo (GRE) planar imaging sequence with the following parameters: 40 axial slices, repetition time (TR) = 2300 ms, echo time (TE) = 30 ms, acquisition voxel size = 3.06 x 2.98 x 3.00 mm^3, slice thickness = 3.0 mm, flip angle = 78°, field of view (FOV) = 220 x 220 x 143 mm^3, acquisition matrix 72 x 73 pixels. The acquisition of the functional volumes was preceded by five dummy scans, resulting in a total acquisition time of approximately 8 min. Participants were instructed to lie still while looking at a fixation cross during the whole resting-state scan. Additionally, T1-weighted high resolution images were collected from the same participants for anatomic normalization: 160 sagittal slices, TR = 8100 ms, TE = 3.7 ms, acquisition voxel size = 1.0 x 1.0 x 1.0 mm^3, flip angle = 8°, FOV = 240 x 240 x 160 mm^3, acquisition matrix 240 x 240 pixels. The whole scanning session lasted approximately 50 minutes and also included task-based fMRI and diffusion tensor imaging which are in preparation for other publications.

3.3.3 fMRI preprocessing and functional connectivity calculation

fMRI preprocessing and feature generation was executed in MATLAB 2017b using the CONN toolbox (V17) (Whitfield-Gabrieli & Nieto-Castanon, 2012). For preprocessing, CONN uses functions from the SPM12 software (V6906) (http://www.fil.ion.ucl.ac.uk/spm/). The following preprocessing steps were performed in succession. 1) Translation of the anterior commissure to the (0,0,0) coordinates. 2) Realignment and unwarping. 3) Slice-timing correction. 4) Outlier detection using the Artifact Detection Tools (http://web.mit.edu/swg/software.htm). 5) Co-registration of the functional image to the individual T1-image. 6) Segmentation and normalization of the T1-image to the Montreal Neurological Institute (MNI) space. 7) Normalization of the functional images using the deformation matrix created in the previous segmentation and normalization of the T1-image. 8) Interpolation to a voxel size of 3 mm x 3 mm x 3 mm. 9) Spatial smoothing with a

Gaussian kernel (8 mm full width at half maximum (FWMH)). Importantly, the spatial smoothing was only applied for the mass-univariate analysis. Spatial smoothing was skipped for MVPA. Following these preprocessing steps, a general linear model was used to remove confounding effects of motion on the blood oxygenation level dependent (BOLD) time series. The CompCor method (Behzadi, Restom, Liau, & Liu, 2007) as implemented in CONN was applied to remove further confounds. CompCor estimates the principal components from the BOLD time series of the white matter and the cerebrospinal fluid which are unlikely to be modulated by neural activity. Removing these principal components using a general linear model thus increases the signal to noise ratio in functional images (Chai, Castañán, Öngür, & Whitfield-Gabrieli, 2012). In addition, the data were band-pass filtered from 0.008 Hz to 0.09 Hz and linearly detrended.

Subsequently, we calculated Integrated Local Correlation (Deshpande, LaConte, Peltier, & Hu, 2009) and Global Correlation as implemented in the CONN toolbox, for each voxel separately. The Integrated Local Correlation represents the average correlation between a given voxel and its neighbor voxels. On the other hand, the Global Correlation represents the average correlation between a given voxel and every other voxel of the brain. Integrated Local Correlation is a measure of local connectivity and Global Correlation is a measure of global network centrality. Thus, these measures reveal complementary information about the topology of the functional brain network. In the following, the Integrated Local Correlation is referred to as *local connectivity* and the Global Correlation is referred to as *global connectivity*. Local and global connectivity maps were then reduced to voxels of the AC, the PFC and the parietal cortex, brain regions which have repeatedly been associated with AP (Hou et al., 2016). The AP-relevant gray matter brain regions were selected from the probabilistic Harvard-Oxford cortical atlas as implemented in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Subsequently, these regions were combined and thresholded at 10 % probability. The AC included the planum temporale, the planum polare, the Heschl's gyrus (HG), and the superior temporal gyrus. The PFC included the inferior frontal gyrus, the middle frontal gyrus (MFG), and the superior frontal gyrus. Finally, the parietal cortex included the supramarginal gyrus, the angular gyrus, and the superior parietal lobule. All brain regions were selected from both hemispheres. The local and global connectivity maps were subsequently used as separate input datasets for the mass-univariate analysis and MVPA.

3.3.4 Mass-Univariate analysis

The connectivity measures were compared between AP and Non-AP musicians using the SciPy package (V0.18.1, (Oliphant, 2007) in Python 2.7.13. Accordingly, at each voxel, we calculated two-tailed two sample t-tests, separately for the local connectivity and the global connectivity as dependent variables. This resulted in statistical maps comprising t-values written to all voxels of the AC, the PFC and the parietal cortex. The statistical significance of these t-value maps was evaluated using the supra-threshold cluster test described below.

3.3.5 MVPA

A linear support vector machine (SVM) as implemented in PyMVPA (V2.6.4) (Hanke et al., 2009) was used to classify AP and Non-AP musicians based on the two connectivity measures. The regularization parameter of the SVM was set to C = 1 and kept constant. The local and global connectivity maps were separately used as input data for the group classification. First, the connectivity maps from all participants were concatenated resulting in a number of participants x number of voxels data matrix with single participants as samples and the connectivity values of single voxels as features. Instead of training the SVM on the whole feature space, we employed a searchlight analysis (Kriegeskorte, Goebel, & Bandettini, 2006). The searchlight analysis used a subset of voxels consisting of a center voxel and surrounding voxels arranged in a sphere as input data to train and test the SVM. We used a relatively large searchlight radius of 3 voxels (9 mm) because i) the spatial extent of the expected effect was not known. ii) Linear SVMs are resistant to the “curse of dimensionality” (i.e., linear SVMs perform well even when the number of features exceeds the number of training examples) (Etzel, Zacks, & Braver, 2013; Jain, Duin, & Mao, 2000). iii) The gray-matter mask restricted the analysis to AP relevant areas (see above) and thus prevented the inclusion of uninformative white-matter and cerebrospinal fluid voxels. Different searchlight sizes were not analyzed. The searchlight sphere was moved through the feature space using each voxel as the center voxel once. The procedure resulted in many thousand searchlights with different input data. In every searchlight sphere, we used the same 5-fold cross-validation scheme where in each fold, 20% of the data was alternately used as the testing dataset and the remaining 80% of the data as the training dataset. Importantly, the amount of AP and Non-AP samples in the testing and training datasets was balanced to avoid sample biases. The classification accuracy of a single searchlight (i.e. the percentage of correctly

classified participants) was defined as the mean accuracy over the five cross-validation folds. This classification accuracy was written to the center voxel of the searchlight to create accuracy maps. The searchlight analysis has the major advantage of being able to localize brain areas with group informative connectivity patterns. The whole analysis resulted in separate accuracy maps for local and global connectivity. The statistical significance of these accuracy maps was evaluated using the supra-threshold cluster test described below.

3.3.6 Supra-threshold cluster test

An identical permutation procedure was used to evaluate the statistical significance of both the t-value maps and the accuracy maps and to correct for the family-wise error (FWE) that arises from multiple testing. The permutation procedure was implemented using custom MATLAB code and is equivalent to the *suprathreshold cluster test* described in Nichols and Holmes (2002). Permutation testing estimates the probability of an empirical result (t-values / accuracies) under the null distribution of no effect. In a two sample case, the null distribution is typically created by randomly permuting the group labels and therefore removing the group information. Accordingly, the mass-univariate analysis and MVPA described above were each repeated 5000 times, but with randomly permuted group labels in each iteration. This resulted in permutation matrices with the permutations in rows and t-values / accuracies from the permutated analyses in columns. Subsequently, we applied a feature-wise threshold ($P < .001$) to both the empirical maps and the permutation matrices to retrieve clusters of high accuracy / t-value voxels. Next, clusters were formed by combining above-threshold voxels converging at least at one face, edge, or corner in the three-dimensional brain space (26-connected neighborhood). The cluster sizes in the maps served as the test statistic *k*. The null distribution of cluster sizes was estimated by storing the maximal cluster size of each permutation. Finally, the *P*-value of a cluster was calculated as the proportion of cluster sizes under the null distribution that were larger or equal than the cluster size of the empirical cluster.

3.4 Results

3.4.1 Pitch-naming ability and musicality

The mean group differences were evaluated using two-tailed Welch's tests in R (V3.3.1) (https://www.r-project.org/). As expected, AP musicians demonstrated substantially higher

pitch-naming scores than Non-AP musicians ($t(98.00) = 13.88$, $P < 10^{-15}$, $d = 2.78$, two-tailed). The density distribution of pitch-naming scores is displayed in Figure 6. This figure shows two separable distributions for AP and Non-AP musicians with some overlap in mid-ranged scores. Although the groups are clearly distinct, some variation in the individual scores is normal and probably unavoidable. Some Non-AP musicians might have used relative pitch specific strategies (e.g. internal rehearsal of tones to calculate the musical interval) to achieve relatively high pitch-naming scores. On the other hand, the mediocre performance of a few AP musicians might be explained by being more familiar with another tuning system than the one employed in this study (A4 = 440 Hz). Also, other factors like motivation and fatigue might have added to the variation in individual pitch-naming scores. Therefore, the pitch-naming scores were used to validate the self-report ofthe participants. Importantly, all AP musicians performed significantly above the chance level of 8.3 %.

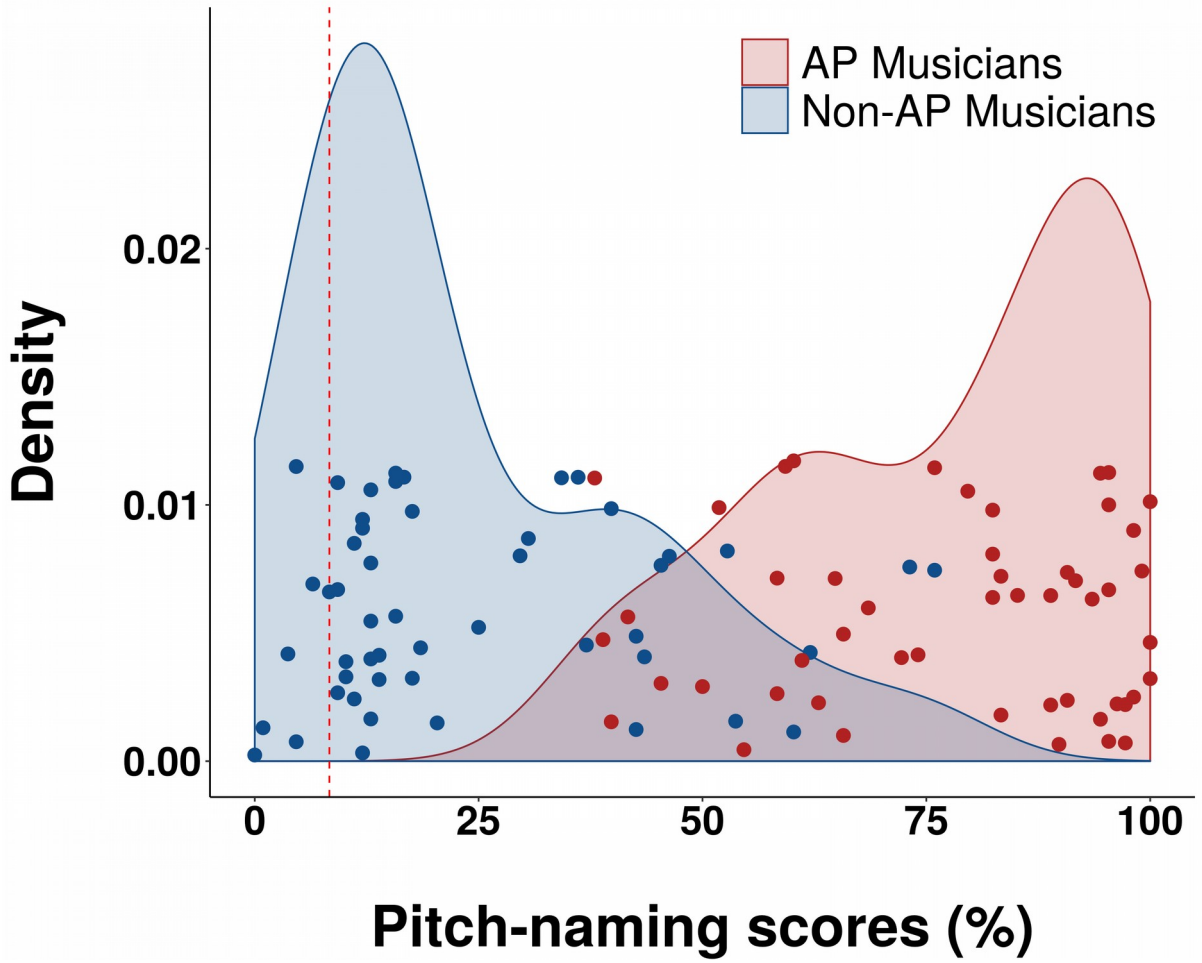

Figure 6: The density distribution of pitch-naming scores for AP musicians (red) and Non-AP musicians (blue). Pitch-naming scores were calculated as the per- centage of correctly labeled tones without counting octave errors. The red, dashed line denotes chance level (8.3%). Individual scores (dots) are jittered along the Y-axis to avoid overlapping data points.

AP musicians and Non-AP musicians did not differ in their musical training in terms of age of commencement of musical training ($t(97.94) = -1.046$, $P = 0.298$, two-tailed) and training effort ($t(92.81) = 1.041$, $P = 0.301$, two-tailed). However, AP musicians had marginally higher AMMA total scores than Non-AP musicians ($t(96.66) = 2.214$, $P = 0.029$, $d = 0.44$,

two-tailed). Post-hoc analyses revealed that AP musicians performed better than Non-AP musicians in tonal judgements ($t(96.09) = 2.467$, $P = 0.015$, two-tailed) but not in rhythmical judgements ($t(97.30) = 1.649$, $P = 0.102$, two-tailed) of the AMMA test. Despite their similar musical training compared to Non-AP musicians, AP musicians might thus have profited from their exceptional pitch encoding abilities to perform better in tonal judgements of the AMMA test. Moreover, the interaction between the factors group and training effort had no significant effect on AMMA total scores ($F(1,96) = 0.008$, $P = 0.930$). With regard to performance in the AMMA test, it is thus very unlikely that AP musicians would have profited in another manner than Non-AP musicians from musical training.

3.4.2 Mass-Univariate analysis

The mass-univariate analysis revealed group differences in both local and global connectivity. As shown in Figure 7A (above), AP musicians showed increased local connectivity in the left inferior part of the MFG ($P = 0.019$, FWE corrected). This cluster comprised 34 voxels with a maximal group difference at the MNI coordinates (x, y, z) -46, 36, 21 ($t(95.92) = 5.16$). Furthermore, as shown in Figure 7A (below), the mass-univariate analysis revealed a cluster of increased local connectivity in AP musicians in the left IPS ($P = 0.044$, FWE corrected) comprising 26 voxels with maximal group difference at the MNI coordinates -40, -39, 40 ($t(97.91) = 4.46$). Finally, as shown in Figure 7B, AP musicians showed increased global connectivity in the right SPL ($P = 0.040$, FWE corrected). This cluster had a size of 40 voxels with maximal group difference at the MNI coordinates 29, -41, 65 ($t(96.52) = 4.24$). We found no clusters in which the Non-AP musicians showed increased local or global connectivity. Significant clusters of increased local and global connectivity in AP musicians are displayed in Figure 7.

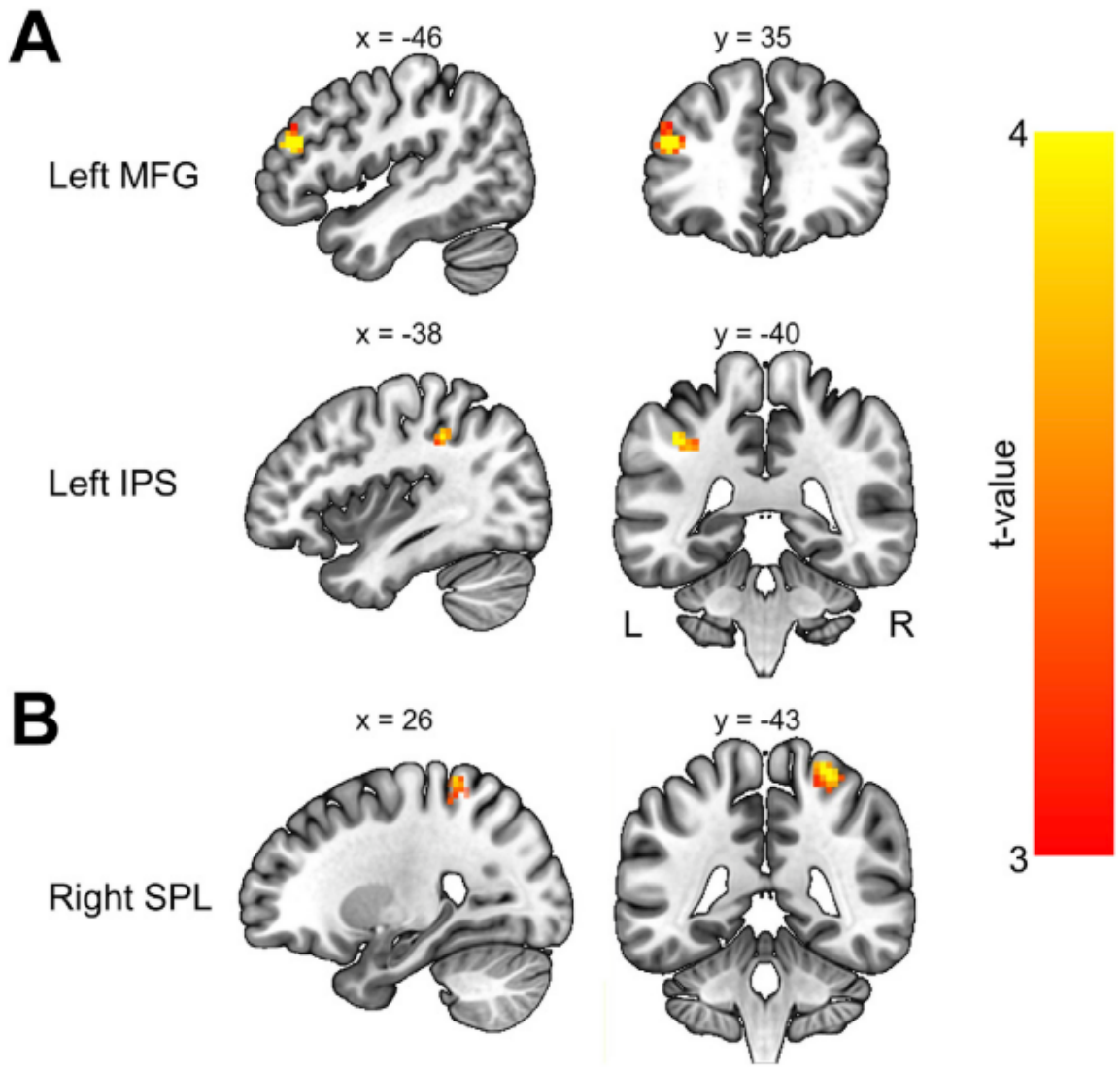

Figure 7: Clusters of increased local connectivity (A) and global connectivity (B) in AP musicians compared to Non-AP musicians. Left middle frontal gyrus (MFG): P¼ 0.019, FWE corrected; cluster size ¼34 voxels. Left intraparietal sulcus (IPS): P¼ 0.044, FWE corrected; cluster size ¼26 voxels. Right superior parietal lobule (SPL): P¼ 0.040, FWE corrected; cluster size ¼ 40 voxels.

We performed two-tailed Pearson correlations to examine whether the connectivity in significant clusters was associated with the performance in our AP test. We restricted this analysis to the group of AP musicians because of two reasons. First, the pitch-naming scores of Non-AP musicians do not reflect their AP ability. Pitch-naming scores of Non-AP musicians are more likely attributable to specific strategies such as rehearsal or guessing, which Non-AP musicians might use to solve this unusual task. Non-AP musicians are thus best excluded from correlative analyses aimed at making inferences about brain-AP ability relationships. Second, a correlative analysis across both groups would be circular since the measure of interest (mean connectivity in significant clusters) was selected on the basis of statistical group differences between AP and Non-AP musicians. No significant correlations between pitch-naming scores and mean cluster connectivity in the left MFG (r = 0.090, P = 0.269), the left IPS (r = -0.007, P = 0.519) or the right SPL (r = 0.045, P = 0.378) were found within the group of AP musicians (see Supplementary Figure 1).

Supplementary Figure 2 displays the descriptive uncorrected mass-univariate t-statistics of local connectivity calculated from smoothed fMRI data (original analysis) and unsmoothed fMRI data. Smoothing imposes similarity on neighboring voxels, reduces variation between such and therefore potentially conceals effects because local connectivity is calculated from neighboring voxels. However, as visually demonstrated in Supplementary Figure 2, smoothing did not conceal potential effects in the mass-univariate analysis of local connectivity. Rather, smoothing enhanced focal differences in local connectivity between AP and Non-AP musicians. For better visualization, the voxel-wise statistics were projected to the brain surface in MNI space.

3.4.3 MVPA

The MVPA of local connectivity patterns revealed above-chance classification. As shown in Figure 8A, AP musicians and Non-AP musicians could be classified significantly above chance level (50%) from local connectivity patterns centered in the left HG (P = 0.030, FWE corrected). This cluster consisted of 16 voxels and was associated with a maximal classification accuracy of 75% at MNI -40, -21, 6. In contrast, the groups could not be classified significantly above-chance based on global connectivity patterns.

To further demonstrate the importance of the fine-grained connectivity patterns for MVPA, we compared the results of the original MVPA of the unsmoothed data to a MVPA of smoothed data. Other than using different input data (unsmoothed vs. smoothed local connectivity maps, both derived from the same unsmoothed fMRI data), we used the exact same procedure for both MVPAs. The groups could not be classified significantly above chance based on smoothed local connectivity. Further, smoothing blurred group informative patterns contained in the fine-grained connectivity profile of the AC. Consequently, smoothing lead to a substantial reduction of group classification accuracy in voxels of the left HG. The mean accuracy (± standard deviation) of the significant cluster in the left HG was 71.75% (±1.69) in the original MVPA based on local connectivity, whereas only 47.50% (±3.75) in the MVPA of the smoothed data. The effect of smoothing on MVPA is demonstrated in Figure 8B. For an improved visualization, voxel-wise p-values for group classification accuracy were projected to the brain surface in MNI space.

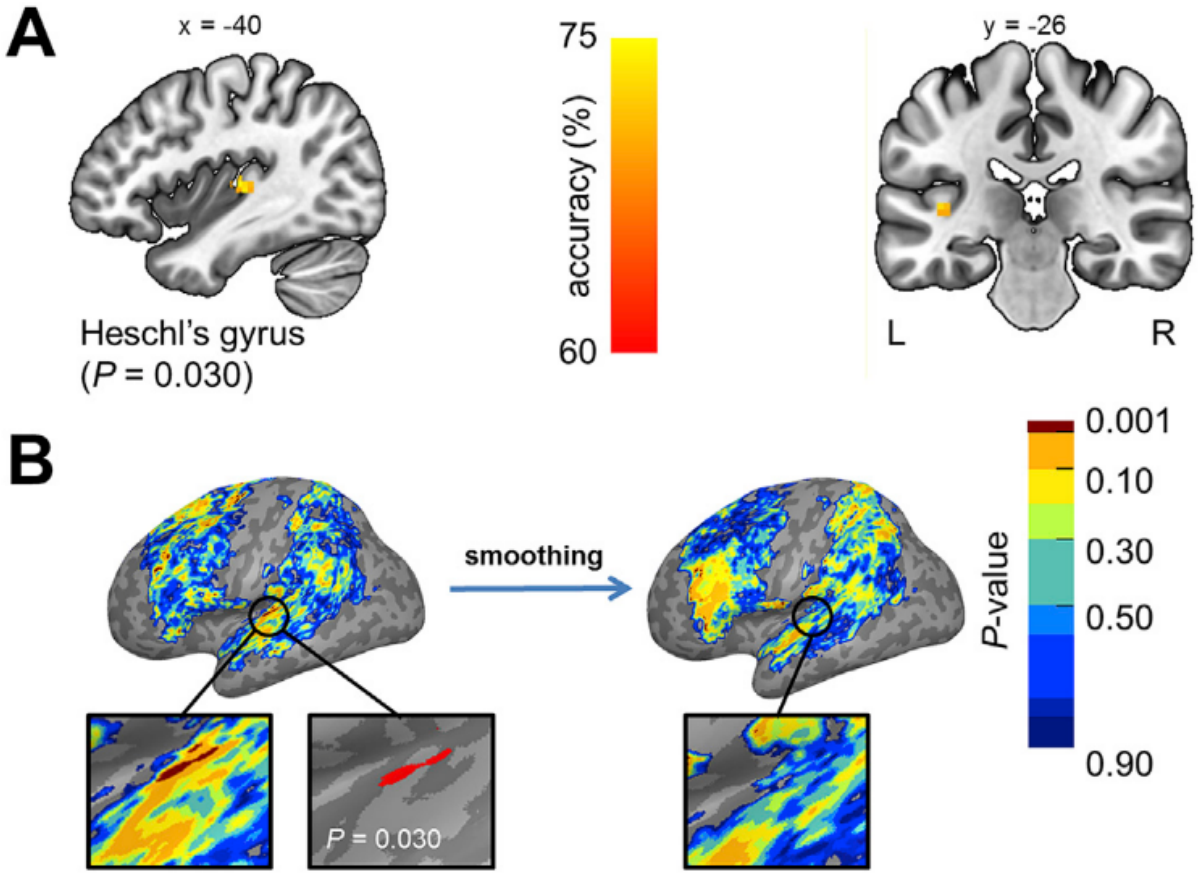

Figure 8: (A) Above-chance classification of AP and Non-AP musicians by the MVPA based on unsmoothed local connectivity in the left Heschl's gyrus (HG) (P = 0.030, FWE corrected; cluster size = 16 voxels; mean accuracy = 71.75%). (B) The effect of smoothing on the MVPA of local connectivity. Smoothing blurs fine-grained complex patterns in the left HG and consequently decreases the classification of AP and Non-AP musicians to chance level. Voxel-wise p-values for group classification accuracy were calculated using 5000 random permutations. Voxels of the significant cluster in the left HG with above threshold (P< 0.001) group classification accuracy are outlined in red.

3.5 Discussion

It has recently been hypothesized that AP ability is enabled by a distributed network (Hou et al., 2016). In the present study, we tested this hypothesis by employing a mass-univariate analysis and MVPA of local and global connectivity measures. The mass-univariate analysis has been used to conform with standard analysis approaches used in most brain imaging studies when group differences in terms of activation and connectivity are evaluated. We also used a multivariate group classification approach (MVPA) based on functional connectivity derived from unsmoothed fMRI data. This approach uses information from multiple voxels to gain deeper insight into the AP-specific connectivity profile (Kriegeskorte & Bandettini, 2007).

Our mass-univariate analysis revealed increased local connectivity in the left MFG and left IPS of AP musicians (Figure 7A). Additionally, AP musicians demonstrated stronger global connectivity in the right SPL (Figure 7B). Thus, this analysis uncovered a different functional resting-state network topology in AP compared to Non-AP musicians, which supports the notion of a specific distributed neural network for AP musicians (Elmer et al., 2015; Hou et al., 2016; Jäncke, Langer, et al., 2012; Kim & Knösche, 2017; Loui et al., 2012b; Oechslin, Meyer, et al., 2010). Our study demonstrates that this AP-specific network is even evident during resting-state when subjects are not involved in musical tasks. How do these findings relate to previously published work on AP? In the following sections, we will discuss our findings in the context of current neuroscience literature on AP.

Twenty years ago, Zatorre et al. (1998) published a paper in which they compared 10 AP with 10 Non-AP musicians using positron emission tomography (PET). They identified peak hemodynamic responses in the left posterior dorsolateral PFC of AP musicians when they listened to musical tones. Moreover, only Non-AP musicians activated the right ventrolateral PFC during an interval labeling task. Therefore, the authors concluded that the posterior dorsolateral PFC is specifically involved in the retrieval of pitch-label associations, whereas the mid-ventrolateral PFC is involved in tonal working memory mechanisms (Bermudez & Zatorre, 2005; Zatorre et al., 1998). Although this clear functional division within the PFC has attracted much research and theoretical contention (Levitin & Rogers, 2005), several studies have reported conflicting findings. For example, the automatic retrieval of pitch-label

associations in AP musicians has also been linked to ventrolateral areas (Wengenroth et al., 2013), and both the mid-ventrolateral and posterior dorsolateral PFC have been associated with tonal working memory (Koelsch et al., 2009; Schulze, Mueller, & Koelsch, 2011; Schulze, Zysset, Mueller, Friederici, & Koelsch, 2011). Thus, the increased local connectivity observed in the anterior part of the left MFG could reflect altered associative memory and/or altered working memory mechanisms of pitch labeling in AP musicians. Since we evaluated resting-state functional connectivity, we are unable to differentiate between these two mechanisms. Future task-based fMRI studies will need to assess the functional division within the PFC in AP.

The parietal areas of the AP-specific network are most likely involved in working memory or multimodal integration processes. Several studies have emphasized the involvement of parietal areas (particularly the IPS) in working memory tasks. The left IPS is recruited during auditory working memory tasks in non-musicians and Non-AP musicians (Schulze, Mueller, et al., 2011; Schulze, Zysset, et al., 2011). Furthermore, activation in inferior parietal areas increased in AP musicians during a tonal working memory task (Schulze et al., 2009). However, IPS activation during this task was spatially more focused in AP musicians than in Non-AP musicians (i.e. a smaller activation cluster in AP musicians). According to the neural efficiency hypothesis (Haier et al., 1988; Neubauer & Fink, 2009), this suggests a more efficient use of tonal working memory in AP musicians. Since neural efficiency could be achieved through neural synchronization (Gotts, Chow, & Martin, 2012), we speculate that increased connectivity/synchronization in the left IPS of AP musicians reflects their efficient use of tonal working memory mechanisms. Such efficiency is possibly mediated by strategies involving both perceptual (pitch) and conceptual (pitch label) information.

The role of the SPL in multimodal integration was demonstrated using human intracranial recordings (Molholm et al., 2006). In this context, higher SPL activation in AP musicians during music listening has been interpreted as the increased engagement of multimodal integration (Loui et al., 2012b). To serve multimodal integration, it is not sufficient that the SPL is active. Additionally, the SPL needs to receive input from multiple areas via global interconnections. Since our results show the global connectedness of the right SPL, we deliver evidence for its qualification as a multimodal integration center in AP. Multimodal integration was more directly studied in audio-visual synesthesia — a phenomenon that shares many

commonalities with AP (Loui, Zamm, & Schlaug, 2012a). In audio-visual synesthesia, inhibition of the right SPL leads to the disruption of automatic tone-color integration (Esterman et al., 2006). This finding further supports our notion that the right SPL is involved in multimodal integration in subjects with altered auditory processing. Moreover, the SPL was found to be globally connected in audio-visual synesthetes during resting-state (Brauchli, Elmer, Rogenmoser, Burkhard, & Jäncke, 2018; Jäncke & Langer, 2011), which is congruent with our AP results.

No significant correlations between brain connectivity and pitch-naming scores emerged within the group of AP musicians. Notably, a behavioral study with more than 2,000 participants suggests that AP musicians represent a distinct population (Athos et al., 2007). This dichotomy of individuals with and without AP would be a direct explanation for the lack of correlations, which is also supported by the distribution of pitch-naming scores in the current study: Figure 6 shows that the pitch-naming scores in our sample are not uniformly distributed, but represent two different distributions for the AP and Non-AP musicians.

In earlier investigations of structural and functional connectivity, AP musicians consistently displayed increased connectivity in the AC (Jäncke, Langer, et al., 2012; Kim & Knösche, 2016, 2017, Loui et al., 2011, 2012b). It is thus noteworthy that our mass-univariate analysis did not reveal increased connectivity in the AC of AP musicians. In contrast to previous studies, we employed a global analysis of connectivity on the voxel level using a strict correction for multiple comparisons. Hence, our mass-univariate analysis might have been too conservative to detect group differences in the AC. However, AP musicians were successfully discriminated from Non-AP musicians by the MVPA based on local connectivity patterns centered in the left HG (Figure 8A). In a previous MVPA study, it has been shown that the type of the perceived sound category (singers, cats, guitars, tones) can be decoded from activation patterns in the AC (Staeren, Renvall, De Martino, Goebel, & Formisano, 2009). This is particularly interesting in the context of AP research since the categorization of sounds by their pitch is thought to be refined in AP musicians (Zatorre, 2003). Moreover, sound category information in the aforementioned MVPA study was undetectable with a conventional mass-univariate analysis. Thus, MVPA might constitute a powerful tool to investigate pitch categorization in AP. Functional alterations in the AC of AP musicians have often been interpreted as evidence for pitch categorization mechanisms. Likewise, we propose

that our finding of altered connectivity patterns in the AC of AP musicians reflects their refined pitch categorization abilities.

Furthermore, we demonstrated the relevance of patterns for MVPA by an MVPA based on smoothed local connectivity (Figure 8B). Smoothing amplifies macroscopic trends in the data, but blurs fine-grained complex patterns. Smoothing decreased group classification accuracy in the left HG to chance level. Thus, we can conclude that the connectivity pattern in the left HG of AP musicians is complex and does not simply reflect macroscopically increased or decreased connectivity.

In conclusion, by examining a relatively large sample of AP and Non-AP musicians, we demonstrate that AP ability is associated with a distributed functional network. This network includes higher-order brain areas (MFG, IPS, and SPL) that are involved in multimodal psychological processing and is not limited to the AC. Moreover, we show for the first time that AP ability can be decoded from connectivity patterns in the AC, which indicates that the fine-grained functional AC architecture differs in AP musicians. We suggest that the perceptual and cognitive mechanisms underlying connectivity alterations in AP require more careful examination in future task-based studies. Also, the imperfect one-to-one correspondence of voxels between participants might have impaired the sensitivity of our between-subject MVPA. Task-based studies could thus profit from a more sensitive within-subject MVPA which is preferably performed in the native subject space.

CHAPTER 4

4 Empirical Part Study III

Brauchli, C., Leipold, S., & Jäncke, L. (2019). Diminished large-scale functional brain networks in absolute pitch during the perception of naturalistic music and audiobooks. (under review)

4.1 Abstract

Several studies have reported effects of absolute pitch (AP) and musical proficiency on the functioning of specific brain areas or distinct subnetworks, but they provide an incomplete account of AP and musical proficiency effects on whole-brain networks. In the present study, we used EEG to estimate source-space functional whole-brain connectivity in a large sample consisting of AP musicians (n = 46), relative pitch (RP) musicians (n = 45), and Non-musicians (n = 34), during resting state, naturalistic music listening, and audiobook listening. The overall connectedness of the participants' functional networks in these states was quantified by the *mean degree* as the average number of connections of every node to every other node in a network. As revealed by cluster-based permutation testing, AP musicians showed a decreased mean degree in relation to Non-musicians whereas RP musicians displayed an intermediate mean degree not statistically different from Non-musicians or AP-musicians. This main effect of group was evident during naturalistic music and audiobook listening, but crucially not during resting state. Moreover, the effect was more pronounced during music than during audiobook listening. Thus, for the first time, we find evidence for diminished functional whole-brain connectivity in AP musicians during the perception of naturalistic auditory stimuli. We suggest that globally diminishing effects on functional connectivity might be mediated by a complex interplay of mechanisms related to AP ability, musical proficiency, music processing and auditory processing per se.

4.2 Introduction

The last decades of neuroscientific research have been influenced remarkably by the realization that "the brain is more than an assemblage of autonomous modules […]" (Sacks, 2011, p. 53). While isolated brain regions show some degree of functional specialization and might be sufficient to control basic functions necessary for survival (e.g., heart rate, breathing), it is striking how higher cognitive functions such as memory, attention, and intelligence are governed by the interactions of multiple brain areas in large-scale networks (Bressler & Menon, 2010; Langer et al., 2012; Mesulam, 1990; Sporns, Chialvo, Kaiser, & Hilgetag, 2004). Therefore, the human brain is nowadays conceived of as a *complex network* which is characterized by robust and highly efficient information transfer between its constituent elements (Bullmore & Sporns, 2009, 2012; Park & Friston, 2013). Since cognitive functions are controlled by large-scale networks, the investigation of musicians with absolute pitch (AP) – the ability to identify a musical pitch without an external reference (Takeuchi & Hulse, 1993) – might be especially suited to study the neural underpinnings of the human brain network. During music production, musicians have to exert virtually every human cognitive function (Münte, Altenmüller, & Jäncke, 2002; Zatorre, 2005), which potentially causes increased functional interactions within and between auditory / sensorimotor networks (Klein et al., 2016; Krishnan et al., 2018; Palomar-García, Zatorre, Ventura-Campos, Bueichekú, & Ávila, 2017; Zatorre, Chen, & Penhune, 2007). In contrast to musicians without AP, musicians with AP additionally use cognitive functions and their underlying functional networks that enable them to effortlessly name and produce musical pitches. It has been suggested that refined pitch categorization is a key property of AP (Levitin & Rogers, 2005; Zatorre, 2003). This perceptual advantage presumably relies on functional and structural alterations in the auditory cortex of AP musicians (Brauchli, Leipold, & Jäncke, 2019; Keenan et al., 2001; Luders et al., 2004; McKetton, DeSimone, & Schneider, 2019; Ohnishi, 2001; Schlaug et al., 1995; Schulze et al., 2009; Wengenroth et al., 2013). Moreover, equal or better performance of AP musicians in tasks requiring tonal working memory, is accompanied by less activation in inferior frontal, middle frontal, and parietal brain areas, compared to RP musicians, (Leipold, Brauchli, Greber, & Jäncke, 2019; Schulze et al., 2009). This could indicate that AP musicians use less neural resources or that they use the same resources but more efficiently (Leipold, Brauchli, et al., 2019). They also may employ different strategies such as associative memory mechanisms not present in RP musicians. These mechanisms might be sustained by the dorsolateral prefrontal cortex (Zatorre et al.,

1998). Accordingly, an AP-specific functional network has been described by increased connectivity within the auditory cortex (Jäncke, Langer, et al., 2012; Kim & Knösche, 2017; Loui et al., 2012b), but also by increased connectivity within parietal and frontal brain areas (Brauchli et al., 2019). Taken together, both musical proficiency and AP ability have observable effects on large-scale functional brain networks and their topology.

To date, most studies have reported alterations with respect to isolated brain areas or distinct functional subnetworks. However, to the best of our knowledge, effects of AP and musical proficiency on whole-brain networks have only been investigated in two studies so far.Investigating structural covariance networks based on anatomical similarities, Jäncke et al. (2012) reported decreased whole-brain connectivity in AP musicians, compared to both RP musicians and Non-musicians. RP musicians and Non-musicians did not differ from each other. This indicates that AP - but not of musical proficiency - has diminishing effects on the whole-brain connectivity. Given that structural covariance networks reflect interactions in functional networks (Evans, 2013), the findings by Jäncke et al. (2012) contrast with the study by Loui et al. (2012b), the second study investigating whole-brain connectivity, reporting increased functional whole-brain connectivity in AP musicians compared to RP musicians. In the present study, we aimed at resolving these contradictory accounts of whole-brain connectivity by a reevaluation of the functional whole-brain connectivity in AP musicians, RP musicians and Non-musicians. In accordance with Jäncke et al. (2012) and Loui et al. (2012b), graph-theoretical network topologogy was assessed by calculating the *mean degree* (i.e. the average number of connections of every node to every other node) in the whole-brain network. Mean degree represents a good measure for the overall connectedness of a network. We extend the aforementioned studies by implementing cluster-based permutation testing (Maris & Oostenveld, 2007; Nichols & Holmes, 2002) – a technique which does not require the choice of a single specific threshold but uses a broad range of connectivity thresholds to evaluate group differences in functional networks. Also, as it is a matter of debate whether effects of AP and musical proficiency are prevalent during resting state (Klein et al., 2016; Loui et al., 2012b; Palomar-García et al., 2017), or if they are only evident during auditory perception (Krishnan et al., 2018), we implemented two naturalistic listening conditions, music and audiobook listening, in addition to resting state. Naturalistic auditory stimuli in an ecological setting without a specific task were used since it has been demonstrated that the human brain processes stimuli in ecological settings differently than in conventional

controlled settings (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). To further assure the ecological validity of our study, functional whole-brain networks were constructed from source-space EEG data, because this allows for a confortable listening experience without inference by acoustic noise.

4.3 Methods

4.3.1 Participants

Studies in neuroscience have recently been criticized for often analyzing data from small samples. Small samples not only reduce the probability of detecting an effect should a true effect exist, but also decrease the probability that a significant result reflects a true effect (Button et al., 2013). Consequently, we analyzed a relatively large sample comprising 46 AP musicians, 45 RP musicians and 34 Non-musicians. All musicians were recruited from local conservatories and orchestras and were professionals, music students, or highly trained amateurs. The assignment to the group of AP or RP musicians was based on self-report and can therefore not be attributed to an arbitrary cut-off in pitch-naming scores. A large part of the sample of AP and RP musicians participated in other EEG and fMRI studies of our research group (Brauchli et al., 2019; Burkhard, Elmer, & Jäncke, 2019; Greber, Rogenmoser, Elmer, & Jäncke, 2018; Leipold, Brauchli, et al., 2019; Leipold, Oderbolz, Greber, & Jäncke, 2019). In this study, we had to exclude seven participants because of unsatisfactory or missing EEG data. In addition to the musicians, we collected data from Non-musicians without musical training to further investigate effects of musical proficiency on functional whole-brain networks. Participants of the three groups were matched for age, sex, handedness, and cognitive capability (see Table III).

TABLE III. Group Demographics Study III

Measure	**AP Mean (±SD)**	**RP Mean (±SD)**	**Non-musician Mean (±SD)**	***P*-value**
Age (years)	26.09 (±4.87)	24.84 (±4.23)	24.29 (±3.42)	.15
Sex ratio (female / all)	0.50 (-)	0.47 (-)	0.51 (-)	.94
Handedness ratio (right / (right + left + ambidextrous))	0.89 (-)	0.89 (-)	0.85 (-)	.85
Cognitive capability[a]	123.26 (±31.14)	134.63 (±26.89)	125.91 (±28.47)	.16
AoC[b] (years)	5.74 (±2.14)	6.40 (±2.47)	-	.18
Training Effort[c] (hours played)	16952 (±12626)	13153 (±9327)	-	.11
AMMA total score[d]	65.98 (±6.39)	62.69 (±6.90)	54.06 (±7.91)	<.001
Pitch-naming score (percent correct)	77.01 (±20.49)	22.08 (±18.18)	6.59 (±4.47)	<.001

[a]Kurztest für allgemeine Basisgrössen der Informationsverarbeitung (KAI) total scores according to (Lehrl, 1992)
[b]Age of commencement of musical training
[c]Training effort measured as total of hours played during lifetime
[d]"Advanced Measures of Music Audiation" (AMMA) according to (Gordon, 1989)

AP and RP musicians were also matched for their musical training in terms of age of commencement and the total of hours played during lifetime (training effort). The musical aptitude of participants was quantified using the "Advanced Measures of Music Audiation" (AMMA) test (Gordon, 1989). In this test, participants need to decide whether 30 successive pairs of short piano melodies are equivalent, different with respect to tonality, or different with respect to rhythmicity. Pitch-naming ability was evaluated using an online adaptation of

an in-house test (Oechslin, Meyer, et al., 2010). In this test, participants had to correctly name a total of 108 pure tones ranging from C3 to B5 (tuning: A4 = 440 Hz). Each tone was presented three times for 500 ms in a pseudo-randomized order, in which the same tone was never presented successively. Tones were preceded and followed by 2 s of Brownian noise. Pitch-naming scores were calculated as the percentage of correctly named tones without counting octave errors.

4.3.2 EEG Recording, Experimental Procedure and Data Preprocessing

EEG data was recorded using a 128-channel HydroCel Geodesic Sensor Net, Net Amps 400 amplifier, and Net Station Acquisition software (Version 5.2.0.2) manufactured by Electrical Geodesic, Inc. (EGI, Eugene, Oregon, USA). The data was collected at a sampling rate of 1000 Hz with Cz as an online reference. The electrode impedances were kept below 25 kΩ by using a potassium-chloride solution. During EEG recording, the participants sat comfortably in a chair in a dimly lit sound-shielded Faraday cage while they rested with their eyes open (EO), listened to excerpts from classical orchestral pieces, and to excerpts from audiobooks played on external speakers. The participants had no specific task but were instructed to fixate a white cross on a black background throughout EO resting-state measurement and acoustic stimulation. As it has been shown that concurrent tasks change both the listening experience and its EEG correlates (e.g. Jäncke, Leipold, & Burkhard, 2018), we explicitly did not use a particular task to keep the listening condition as natural as possible. Our intention was to identify the neural underpinnings of natural music listening in the three subjects group. The musical stimuli were previously used in other publications of our research group and are known to evoke the emotion fear (Gustav Holst: *Mars - the Bringer of War from the Planets*), sadness (Samuel Barber: *Adagio for Strings*), and joy (Beethoven: *Symphony no. 6*) (Baumgartner, Esslen, & Jäncke, 2006; Baumgartner, Lutz, Schmidt, & Jäncke, 2006). The audiobook excerpts were taken as a control condition to the musical stimuli as we wanted to ensure that the effects of music listening were not due to emotional processing evoked by the music, but due to the acoustic stimulation in general. Thus, the audiobooks were chosen according to their potential to evoke the emotion fear (Steven King: *It*), sadness (Nicholas Sparks: *The Choice*), and joy (*Der Kleine Nils*). The audiobook excerpts were presented in German in which all participants were fluent. The auditory stimuli had a duration of three minutes each and were presented in pseudo-randomized order after three minutes of EO resting-state measurement. The pseudo-randomization followed the rule that auditory stimuli

of the same kind were always presented successively, i.e. in music or audiobook blocks. The order of blocks and the order of auditory stimuli within these blocks were randomized. Immediately after the presentation of an auditory stimulus, the participants were required to rate their perceived emotional valence and arousal using the self-assessment manikin (SAM; with nine levels: -4 – +4 [valence] and 0 – 8 [arousal]) (Bradley & Lang, 1994). Furthermore, participants were asked to identify the emotion inherent to the auditory stimulus in a single choice format with the options anger, joy, fear, disgust, and sadness. The whole procedure lasted for approximately thirty minutes.

EEG data recorded during EO resting state or during auditory stimulation were preprocessed in Brain Vision Analyzer (Version 2.0, Brainproducts, Gilching, Germany). After the exclusion of twenty outer electrodes prone to muscle artefacts, a band-pass filter with a high-/low-pass criterion of 0.5/60 Hz (infinite impulse filter, Butterworth, 48 dB/oct) and a notch filter of 50 Hz were applied. Eye movement artefacts (blinks and saccades) were then removed using independent component analysis (Jung et al., 2000) and the remaining bad electrodes were interpolated by spherical splines. Next, the data was re-referenced to the average of all remaining electrodes before EEG segments containing residual artefacts were automatically rejected. Based on the onset of EEG artifacts in single electrodes, surrounding EEG epochs (-200 ms to +200 ms) were rejected from all electrodes by applying the following criteria: a minimal/maximal allowed absolute difference of 0.5/120 µV between the two sample points with lowest and highest amplitude within a time window of 200 ms, minimally/maximally allowed amplitudes of -120/+120 µV at any data point. Based on the amount of remaining (good) EEG segments, data from auditory stimuli evoking joy (Beethoven: Symphony no. 6 & Der Kleine Nils) were excluded from further analyses due to the insufficient data quality during the presentation of the audiobook (which might have been caused by laughing and associated muscle artifacts). Finally, the data was segmented according to the length of the stimuli and further split into epochs of 2 seconds. These epochs were exported for the graph-theoretical network analysis of functional connectivity in the source space (see below).

4.3.3 Graph-theoretical analysis of intracranial functional whole-brain connectivity

The sLORETA toolbox (V20160611) (http://www.uzh.ch/keyinst/loreta.htm) (Pascual-Marqui, 2002) was used for the computation of the source-space functional connectivity (Lai, Demuru, Hillebrand, & Fraschini, 2018). Since low and high EEG frequencies have been related to auditory processing and memory functions (Bastiaansen, Magyari, & Hagoort, 2010; Edagawa & Kawasaki, 2017; Klimesch W., 1997; Klimesch, Schimke, & Schwaiger, 1994; Mai, Minett, & Wang, 2016; Pesonen, Björnberg, Hämäläinen, & Krause, 2006; Yordanova, Kolev, & Başar, 1998), functional connectivity was evaluated in three EEG frequency bands of interest: theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz). Eighty-four nodes used in previous publications of our research group (e.g. Klein et al., 2016) were defined using the centroid voxels of Brodmann areas (BAs) as implemented in sLORETA (42 BAs in each hemisphere). Functional connectivity between these nodes was quantified using *phase synchronization* which is defined as “the absolute value of the complex valued (hermitian) coherency between the normalized Fourier transforms” (Pascual-Marqui, 2007, p. 10), and takes a value between 0 (no synchronization) and 1 (perfect synchronization). Phase synchronization was computed separately for the EO resting-state and each auditory stimulus based on the cross-spectra between EEG epochs before aggregating and averaging by block. As described above, auditory stimuli evoking joy were excluded (see above). This resulted in 84x84 square connectivity matrices, whereas a single cell contained the single participants phase synchronization in a given frequency between two nodes during EO resting state, music listening or audiobook listening. Exemplary difference connectivity matrices between Non-musicians, RP musicians and AP musicians are displayed in Figure 9.

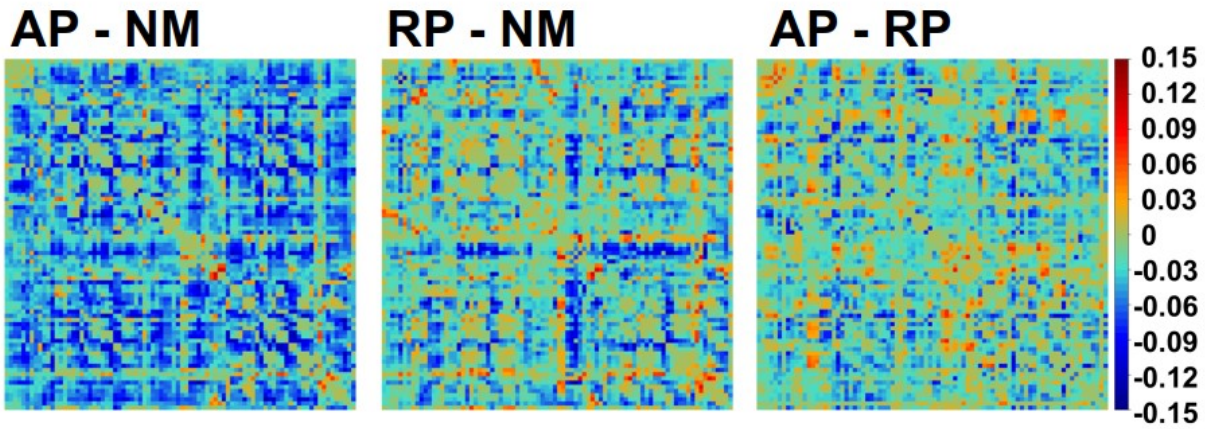

Figure 9. Source-space functional connectivity between 84 regions of interest, derived from the beta frequency band during music listening. Displayed are difference connectivity matrices between AP musicians (AP), RP musicians (RP) and Non-musicians (NM).

The single participants' connectivity matrices were further processed using custom MATLAB code and functions of the Brain Connectivity Toolbox (V20170115) (http://www.brain-connectivity-toolbox.net) (Rubinov & Sporns, 2010). For each participant in each block and frequency band, the connectivity matrices were thresholded over a wide range of phase synchronization values from 0.1 to 0.9 in increments of 0.05. Subsequently, the *mean degree* of each thresholded matrix was computed as the average number of connections of every node to all connected other nodes in the network. This procedure yielded 17 mean degree values for each participant in each block and frequency, which was equivalent to the number of employed phase synchronization thresholds (0.1 – 0.9).

Group differences in mean degree across 17 contiguous phase synchronization thresholds were examined separately for block (EO resting state, music block, audiobook block) and frequency (theta, alpha, beta). Conventional parametric statistical tests are not suited to assess group differences in graph-theoretical measures across multiple thresholds since the assumption of statistical independence is not given (Jäncke, Langer, et al., 2012; Langer, Pedroni, & Jäncke, 2013). Group differences in graph-theoretical measures have hence been evaluated at a single threshold in previous studies (Loui et al., 2012b). The choice of the threshold in such an analysis, however, is arbitrary and the analysis yields no information about the stability of the effect across multiple thresholds. Therefore, cluster-based

nonparametric permutation testing, commonly used for the evaluation of spatially or temporally dependent fMRI/EEG data (Maris & Oostenveld, 2007; Nichols & Holmes, 2002), was employed to examine the statistical significance of group differences in mean degree and to correct for the family-wise error (FWE) that arises from multiple testing across different thresholds (Drakesmith et al., 2015; Langer et al., 2013). In this test, the probability of *clustered* mean degree differences (i.e. differences across multiple contiguous phase synchronization thresholds) was estimated under the null distribution of no effect. This null distribution of no effect was created by randomly permuting group labels and therefore removing group information. In detail, empirical mean degree differences at separate phase synchronization thresholds were first calculated using a one-way analysis of variance (ANOVA in R (V3.3.1; https://www.r-project.org/)) with the single between factor Group (AP musicians, RP musicians, Non-musicians). Next, group labels were permuted in n = 5000 iterations before calculating random group differences in mean degree for each permutation at each phase synchronization threshold using an identical ANOVA. Importantly, statistical dependency across contiguous phase synchronization thresholds was preserved in permutations; i.e. for a given permutation iteration, the random assignment of group labels was identical for all phase synchronization thresholds. Next, statistical values lower than $P < .05$ and emerging at contiguous phase synchronization thresholds were combined to clusters. Note that in this case, the *P*-value is used as a descriptive cluster-defining threshold and not for inference. The cluster size in the empirical data served as the test statistic *k*. The null distribution of cluster sizes was estimated by storing the maximal cluster size of each permutation. Finally, the *P*-value of the empiric cluster was calculated as the proportion of cluster sizes under the null distribution that were larger than *k*.

4.4 Results

4.4.1. Pitch-naming ability and musical proficiency

A one-way ANOVA was conducted to examine the effect of Group (AP musicians, RP musicians, Non-musicians) on pitch-naming and AMMA total scores. As expected, the effect of Group on pitch-naming scores was highly significant ($F(2,122) = 205.71$, $P < 10^{-15}$, $\eta 2 = 0.77$). Post-hoc two-tailed Welch's tests revealed that AP musicians demonstrated substantially higher pitch-naming scores than both, RP musicians ($t(88.17) = 13.54$, $P < 10^{-15}$, $d = 2.83$) and Non-musicians ($t(50.70) = 22.59$, $P < 10^{-15}$, $d = 4.45$). Also, RP musicians

demonstrated higher pitch-naming scores than Non-musicians ($t(50.90) = 5.50$, $P < 10^{-5}$, $d = 1.10$)(Figure 10). This suggests that some RP musicians might have used relative pitch specific strategies (e.g. internal rehearsal of tones to calculate the musical interval) to achieve relatively high pitch-naming scores in comparison to untrained Non-musicians, as we have already suggested in a previous publication of our research group (Brauchli et al., 2019).

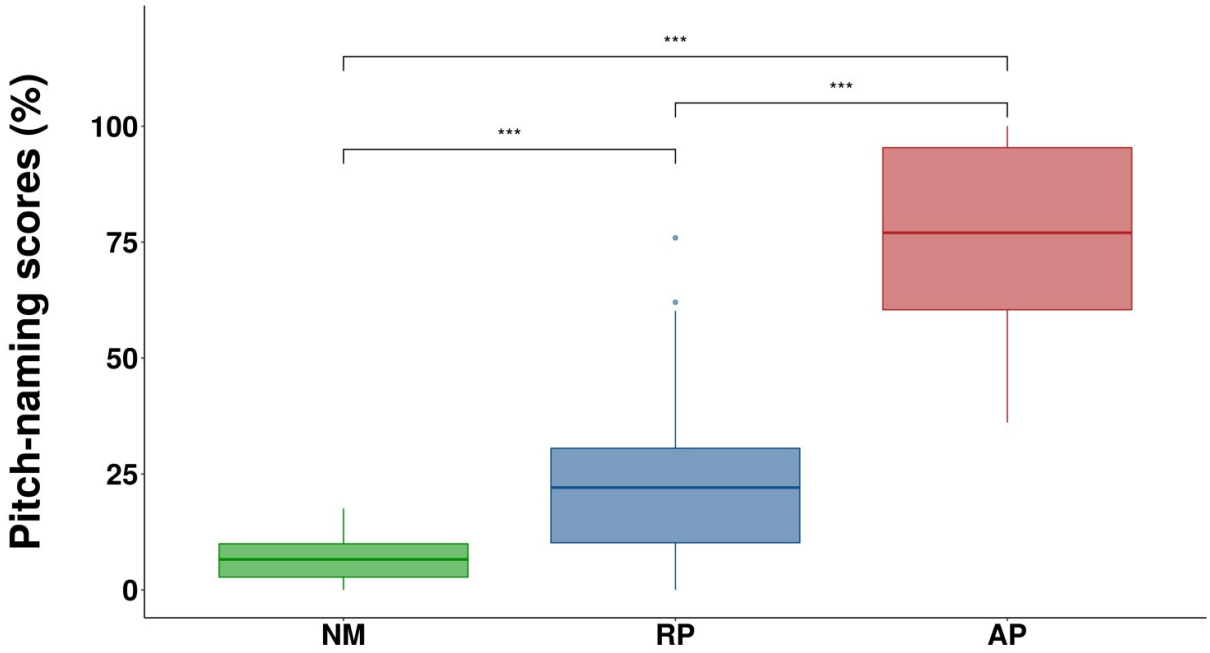

Figure 10. Pitch-naming scores for Non-musicians (NM), RP musicians (RP) and AP musicians (AP). Asterisks denote significant group differences (*p < 0.05, **p < 0.01, ***p < 0.001).

Furthermore, the analyses revealed a significant effect of Group on AMMA total scores ($F(2,122) = 29.18$, $P < 10^{-10}$). As expected, Non-musicians performed significantly worse than AP musicians ($t(61.95) = -7.22$, $P < 10^{-9}$, $d = -1.69$) and RP musicians ($t(65.61) = -5.07$, $P < 10^{-5}$, $d = -1.17$). AP musicians had marginally higher AMMA total scores than RP musicians ($t(88.13) = 2.36$, $P = 0.021$, $d = 0.49$). This effect was driven by the better performance of AP musicians than RP musicians in tonal judgements ($t(87.02) = 2.69$, $P = 0.009$), but not in rhythmical judgements ($t(88.90) = 1.69$, $P = 0.095$). The enhanced performance of AP

musicians in tonal judgements of the AMMA test might be explained by their exceptional pitch encoding abilities. The groups did not differ in their musical training in terms of age of commencement of musical training ($t(86.69) = 1.36$, $P = 0.177$) and training effort ($t(82.84) = 1.63$, $P = 0.106$). Since most of the Non-musicians did not report having received a musical training in their lifetime, age of commencement of musical training and training effort were not statistically evaluated for Non-musicians. All Non-musicians with some sort of musical experience reported a training effort of less than 4000 hours over their lifetime.

4.4.2. Emotional judgements of music and audiobooks

The majority of the participants correctly identified the emotion fear after having listened to the fear evoking musical stimulus (52.46 % correct) or audiobook (61.48 % correct), as opposed to the guessing level of 20 % (single choice format with five options, see above). In wrong emotion judgements, fear was mostly confused with the negative emotions anger (musical stimulus) or disgust (audiobook). Moreover, the participants were highly accurate in identifying the sadness evoking musical (88.52 %) and audiobook stimulus (97.54 %). In contradiction to their high accuracy in identifying negative emotions, many participants reported having experienced positive (Valence rating > 0) emotions during music listening (fear: 64.75 %, sadness: 34.43 % of participants). This discrepancy between objectively recognized and subjectively experienced emotional valence was less evident for audiobooks (fear: 13.93 %, sadness: 2.46 % of participants with positive valence ratings).

An ANOVA was conducted to examine the main effects of Group (AP musicians, RP musicians, Non-musicians) and Block (music, audiobook) and the interaction between Group and Block on arousal ratings. The analysis yielded a significant effect of Block ($F(1,119) = 151.51$, $P < 10^{-15}$) with higher arousal ratings for music (mean = 5.27 ± 1.94) than for audiobook blocks (mean = 3.20 ± 1.94). Moreover, the analysis yielded a significant interaction between Group and Block ($F(2,119) = 8.65$, $P < 0.001$). Post-hoc analyses revealed that this interaction effect was driven by lower music block arousal ratings of Non Musicians (mean = 4.42 ± 1.72) in comparison to both, AP musicians (mean = 5.79 ± 1.76) ($t(68.98) = 3.99$, $P < 0.001$) and RP musicians (mean = 5.39 ± 2.07) ($t(73.79) = 2.59$, $P < 0.05$). Arousal ratings for audiobook blocks did not differ between groups. (Figure 11).

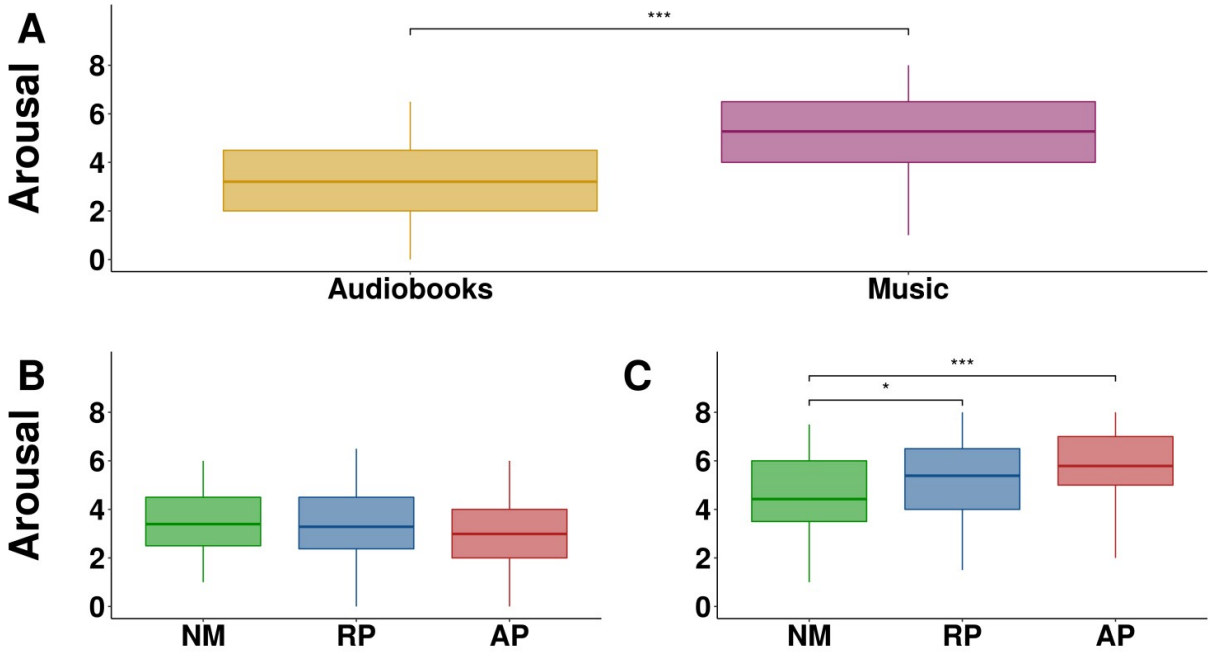

Figure 11. (A) Mean emotional arousal ratings for audiobooks and music. (B) & (C) Perceived emotional arousal in Non-musicians (NM), RP musicians (RP) and AP musicians (AP) when listening to audiobooks (B) or music (C). Asterisks denote significant differences (*p < 0.05, **p < 0.01, ***p < 0.001).

4.4.3. Graph-theoretical analysis

Group differences in the mean degree of functional networks during resting state, music listening, and audiobook listening were assessed using the cluster-based permutation testing procedure described above. The analysis yielded a significant effect of Group (AP musicians, RP musicians, Non-musicians) on the mean degree derived from the beta frequency band exhibited during music listening (P = 0.014, FWE corrected), with a cluster extent of 14 contiguous phase synchronization thresholds from 0.1 to 0.75. This effect was driven by the lower mean degree of AP musicians than Non-musicians at any threshold from 0.1 to 0.75 ($t(78) > 2.64$, $P < 0.01$). RP musicians did not significantly differ from Non-musicians ($t(77) < 1.99$, $P > 0.05$) or AP musicians ($t(89) < 1.99$, $P > 0.05$) at any phase synchronization threshold. (Figure 12).

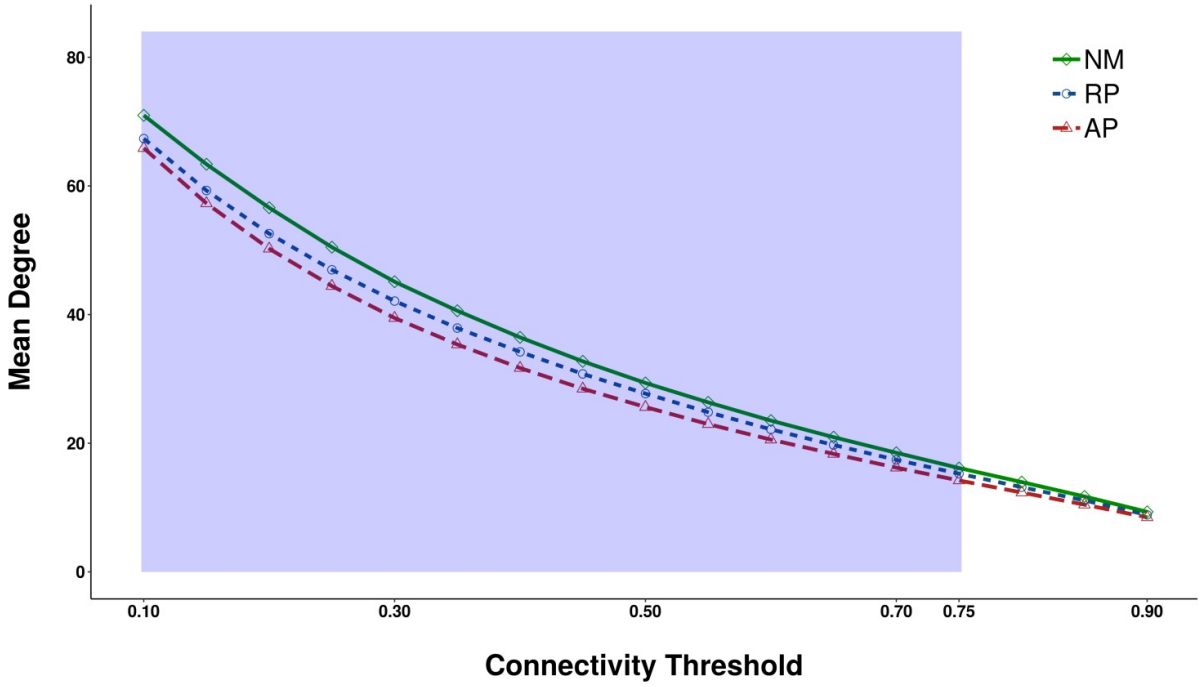

Figure 12. The mean degree of Non-musicians (NM), RP musicians (RP) and AP musicians (AP) derived from the beta frequency band exhibited during music listening. Cluster-based permutation testing revealed a group effect across a broad range of connectivity thresholds (P = 0.014, FWE corrected, blue shaded area). This effect was driven by the decreased mean degree of AP musicians in relation to Non-musicians at every threshold ranging from 0.1 to 0.75 ($t(78) > 2.64$, $P < 0.01$).

The analysis further revealed a significant effect of Group on the mean degree derived from the beta frequency band exhibited during audiobook listening (P = 0.045, FWE corrected, 5 contiguous thresholds from 0.1 to 0.3). This effect was driven by the lower mean degree of AP musicians than Non-musicians ($t(78) > 2.64$, $P < 0.01$), whereas RP musicians did not significantly differ from Non-musicians or AP musicians. No significant effect of Group on the mean degree derived from the beta frequency band exhibited during resting state (P = 0.148, FWE corrected) was found. Also, no significant effect of Group on the mean degree derived from the theta or alpha frequency band was found.

Post-hoc two-tailed pearsons correlations were performed to evaluate whether the mean degree of AP musicians, RP musicians or Non-musicians during music listening was related to their pitch-naming ability, musical aptitude, or their music block arousal rating. The analysis revealed no significant correlation between the mean degree averaged across thresholds from 0.1 to 0.75 and pitch-naming scores of AP musicians (r = -0.18, P = 0.228), RP musicians (r = -0.12, P = 0.448) or Non-musicians (r = -0.14, P = 0.425). Similarly, no significant correlation between the mean degree and AMMA total scores of AP musicians (r = 0.02, P = 0.908), RP musicians (r = 0.04, P = 0.799) or Non-musicians (r = -0.31, P = 0.075) was found. Finally, the analysis yielded no significant correlation between the mean degree and music block arousal ratings of AP musicians (r = -0.13, P = 0.384), RP musicians (r = -0.16, P = 0.285) or Non-musicians (r = -0.16, P = 0.369).

4.5 Discussion

Previous investigations have studied the effects of AP and musical proficiency on specific brain areas or distinct functional subnetworks (Brauchli et al., 2019; Kim & Knösche, 2016; Klein et al., 2016; Loui et al., 2011; Palomar-García et al., 2017). These investigations provide incomplete insight on effects on a whole brain network. Also, it is unclear whether or not effects of AP and musical proficiency are only evident during music listening (Klein et al., 2016; Krishnan et al., 2018; Loui et al., 2012b). Using graph-theoretical network topology and cluster-based permutation testing, we assessed effects of AP and musical proficiency on functional whole brain functional connectivity during resting state, music listening, and audiobook listening. Our analyses revealed a significant effect of Group on the mean degree of a functional network derived from the beta frequency band during both music and audiobook listening, but not during resting state. This effect was descriptively more extensive during music listening (cluster size = 14) than during audiobook listening (cluster size = 5). Also, group differences during auditory perception were driven by a decreased mean degree in AP musicians in relation to Non-musicians, whereas RP musicians displayed an intermediate mean degree not statistically different from Non-musicians or AP musicians.

Thus, for the first time, we find evidence for diminished functional whole brain connectivity in AP musicians, consistent with a previous finding of AP musicians' globally decreased structural covariance networks (Jäncke, Langer, et al., 2012). In contrast to the previous study,

our results however indicate that decreased whole brain connectivity in AP musicians is not a mere consequence of their AP ability. More likely, diminishing effects on global functional interconnections were mediated through mechanisms related to AP ability, musical proficiency, music processing and auditory processing per se.

One such mechanism might have operated through the interaction between AP ability and the special role of pitch in music. Pitch constitutes a primary dimension of music (Krumhansl, 2000) and varies far more subtly in music than in speech where it is used for the purpose of intonation (Zatorre & Baum, 2012; Zatorre, Belin, & Penhune, 2002). The superior pitch processing abilities of AP musicians might thus have been most effectual during music listening which may explain their greatest divergence in functional connectivity during this condition. Furthermore, influences of musical proficiency are indicated by the intermediate connectivity of RP musicians and might relate to the musicians' cognitive benefit in functions such as auditory memory (Nunn et al., 2002; Pallesen et al., 2010), auditory-motor integration (Baumann et al., 2007; Zatorre et al., 2007), and syntactic processing (Fitzroy & Sanders, 2013). Notably, these cognitive functions are relevant for both music and speech processing (Besson, Chobert, & Marie, 2011; Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Patel, 2003), and have been related to the beta frequency band (Bastiaansen et al., 2010; Edagawa & Kawasaki, 2017; Mai et al., 2016; Pesonen et al., 2006). Diminished beta coupling during music and audiobook listening but not during resting state might thus indicate the musicians' neural efficiency when such cognitive functions are stimulated. In that regard, our interpretation of decreased functional connectivity is congruent with a previous interpretation of decreased brain activity in AP musicians as an example of neural efficiency (Leipold, Brauchli, et al., 2019).

Apart from cognition, one could argue that emotional processes had an impact on functional networks. Particularly as group differences in beta coupling seemed remarkably well contrasted by the groups' emotional response to music, which was generally more intense than to audiobooks. Higher emotional intensity might be attributed to the increased potential of music to evoke complex emotions, as it is indicated by the discrepancy between recognized and subjectively experienced emotional valence. This phenomenon is best described by paradox and ergo complex emotions like a "beautiful sadness" or a "invigorating fear", and might have affected the participants' beta coupling during music listening. However,

emotional processing is more strongly associated with lower frequencies of the human EEG, especially alpha (Baumgartner, Esslen, et al., 2006; Harmon-Jones, Gable, & Peterson, 2010), in which no connectivity differences were found. Moreover, group differences in beta coupling were also evident during audiobook listening for which participants reported a comparable degree of emotional arousal. We therefore propose the aforementioned cognitive mechanisms during auditory processing as the most likely cause of the AP musicians' decreased whole brain connectivity although influences of emotion are also conceivable. The lack of correlation between the AP musicians' functional connectivity and their pitch-naming ability as well as their musical aptitude indicates a complex brain-cognition relationship rather than one single driving mechanism.

Our results stand in contrast to a previous report of enhanced functional whole-brain connectivity in AP musicians by Loui et al. (2012b). This divergence might be caused by methodological differences between the studies. In the aforementioned study, correlation matrices were averaged across subjects to obtain a mean functional network for AP musicians and RP musicians. Group differences in whole brain functional connectivity were then assessed in a statistical model with the AP and RP networks' single nodes as observations. Such an approach might not conform with the assumption of statistical independence between observations and defines its statistical power through network size rather than by sample size. As we analyzed group differences on the basis of the individual subjects' whole-brain connectivity with individual participants as observations, the approach used our study more likely characterizes an AP-specific large-scale brain network.

In conclusion, we demonstrate globally diminished functional networks of AP musicians during auditory processing and especially during music listening. Due to the comparatively low spatial resolution of EEG and numerous previous studies on specific brain areas that might underly the AP ability, we refrain from making statements about the brain areas constituting the AP-specific networks or subnetworks. The influence of cognitive and emotional mechanisms on the AP musicians' functional network requires more careful examination in future specifically designed studies.

4.7 Conflict of interest

None.

CHAPTER 5

5 General Discussion

In the present thesis, functional networks in AV synesthesia and in AP were investigated. It has been demonstrated that networks in AV synesthesia and AP are characterized by increased functional connections within subnetworks or specific brain areas respectively. AV synesthetes in Study I demonstrated a subnetwork of increased RS functional connectivity encompassing auditory, visual and parietal brain areas, whereas AP musicians showed increased functional RS connectivity within parietal and frontal brain areas in Study II. Since these connectivity increases were prevalent during RS, they might reflect the baseline from which neurophysiological processes start upon auditory perception in AV synesthesia and AP. During auditory perception, AP musicians in Study III showed globally diminished functional networks. This effect of AP on functional whole-brain connectivity was not evident during RS.

5.1 Network characteristics in AV synesthesia and AP

AV synesthesia and AP refer to enhanced auditory perception and often co-occur in the same individuals (Cytowic & Eagleman, 2009). It has hence been suggested that AV synesthesia and AP are “two sides of the same coin” (Loui et al., 2012a, p. 1,6) relying on similar neural mechanisms. Accordingly, the authors of the aforementioned study have shown that AV synesthetes and AP musicians both demonstrate increased activation of the secondary AC during music listening, as opposed to control subjects with neither of the two abilities.

The present thesis provides further evidence for the involvement of the AC in AV synesthesia and AP by showing that functional connections within the AC during RS are altered in both phenomena. However, contrary to the statement by (Loui et al., 2012a), our results point towards different neural mechanisms of the AC underlying AV synesthesia and AP. In AP research, functional and structural alterations of the AC (Keenan et al., 2001; Luders et al.,

2004; Ohnishi, 2001; Schlaug et al., 1995; Schulze et al., 2009; Wengenroth et al., 2013; Zatorre et al., 1998) have mostly been related to the refined pitch categorization ability of AP musicians (Zatorre, 2003). The notion of enhanced pitch categorization in AP is further supported by our finding of altered connectivity patterns in the left AC of AP musicians (Study II). Indeed, the activation of the AC is associated with the encoding of sound categories (Belin et al., 2000; Lewis et al., 2005) and specific sound categories can be decoded from activation patterns in the AC (Staeren et al., 2009). To the author's knowledge, AV synesthetes have never been related to a refined pitch categorization ability. AC activity in AV synesthesia is most probably modulated through feedback loops from higher-order (Grossenbacher & Lovelace, 2001) or visual (Smilek, Dixon, Cudahy, & Merikle, 2001) brain areas which coincides with our finding of widespread functional connections of the AC and top-down pathways in AV synesthesia (Study I).

The involvement of the parietal lobe in AV synesthesia and AP (Study I & Study II) on the other hand may be attributable to similar *binding* mechanisms. Binding refers to multimodal integration and explains how humans perceive the world as a unified whole although physical properties of stimuli (e.g. color, size, shape, motion) are initially processed in separate brain areas (Robertson, 2003). It has been hypothesized that the parietal lobe is crucial for the integration of color and shape in grapheme-color synesthesia (Esterman et al., 2006). In accordance with this hypothesis, the inhibition of the right superior parietal lobe with transcranial magnetic stimulation transiently attenuates the synesthetic binding of color and shape (Esterman et al., 2006). Binding mechanisms have been confirmed in different forms of synesthesia (Bien, Oever, Goebel, & Sack, 2012; Esterman et al., 2006; Hubbard, 2007; Smilek, Dixon, & Merikle, 2005) and it is likely that binding is also essential for the integration of tone and color in AV synesthesia. Likewise, the parietal lobe might serve the binding of pitch and label in AP. Especially since pitch-label associations in AP musicians seem to be automatic and not suppressible even if it is disadvantageous for the task at hand (Itoh et al., 2005; Miyazaki & Rakowski, 2002; Schulze, Mueller, & Koelsch, 2013), as if pitch and label were inseparable from each other. It is thus not surprising that the increased activation of the parietal lobe in AP musicians during music listening has previously been related to binding mechanisms (Loui et al., 2012b). In Study II we provided further evidence for the qualification of the parietal lobe as multimodal binding center in AP by demonstrating its capability to receive input from various brain areas, which points to its global connectedness. This was also evident in a descriptive seed-based approach - the right superior

parietal lobe in AP musicians has generally more suprathreshold connections than in RP musicians across various cluster-forming thresholds (Figure 13). Moreover, connections from the right superior parietal lobe to the frontal cortices, which are implicated in generating pitch-label associations (Bermudez & Zatorre, 2005; Zatorre et al., 1998), remain at the threshold of highest stringency in AP musicians. It is thus imaginable that pitch-label associations of AP musicians are first generated in frontal cortices and then forwarded to the right superior parietal lobe where these associations are unified to one holistic experience.

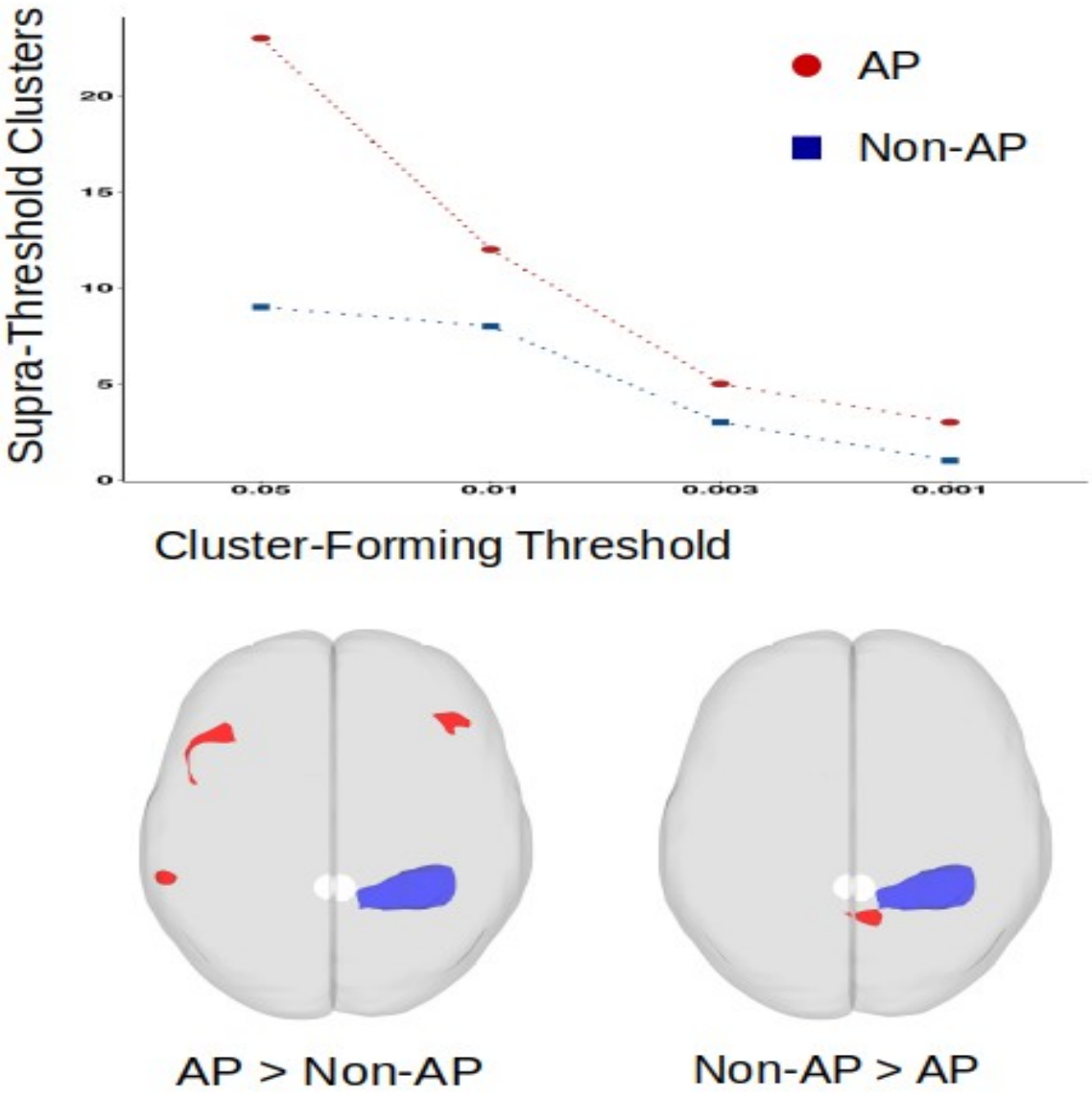

Figure 13. Descriptive connectivity analysis seeding from the right superior parietal lobe. (Top) AP musicians display generally more supra-threshold connections than Non-AP musicians across various cluster-forming thresholds. (Bottom) Supra-threshold clusters at the threshold of highest stringency (0.001). The right superior parietal lobe is marked in blue.

The brain networks in AV synesthesia and AP can also be compared in terms of their topology. Brain networks are organized as so-called *small-world* networks, characterized by a high degree of local clustering between neighboring nodes but relatively few long-range connections (Bassett & Bullmore, 2006), enabling economical but efficient information transmission between brain areas (Bullmore & Sporns, 2012; Latora & Marchiori, 2001). The AP brain network as a case of local hyperconnectivity (Study II) (Jäncke, Langer, et al., 2012; Kim & Knösche, 2016, 2017, Loui et al., 2011, 2012b) but global hypoconnectivity (Study III) (Jäncke, Langer, et al., 2012), might thus constitutes an example of increased small-world properties and of **efficient** information transmission between brain areas. In comparison, the AV synesthesia brain network, which is described by global hyperconnectivity (Study I) (Hänggi et al., 2011), rather constitutes an example of **easy** information transmission through strong and numerous connections.

5.2 Conclusion and objectives for future studies

Our results support both, distinct and shared functional brain network characteristics in AV synesthesia and AP. The most notable shared neural characteristic is the involvement of the parietal lobe which might serve the binding of pitch and label in AP, as it serves the binding of inducer and concurrent perception in synesthesia. Inspired by research in synesthesia, transcranial magnetic stimulation might be used to further investigate the role of the parietal lobe as a multimodal integration center in AP. Likewise, our analyses of directed connectivity in AV synesthesia might be adapted to investigate causal relationships between brain areas in AP.

6 References

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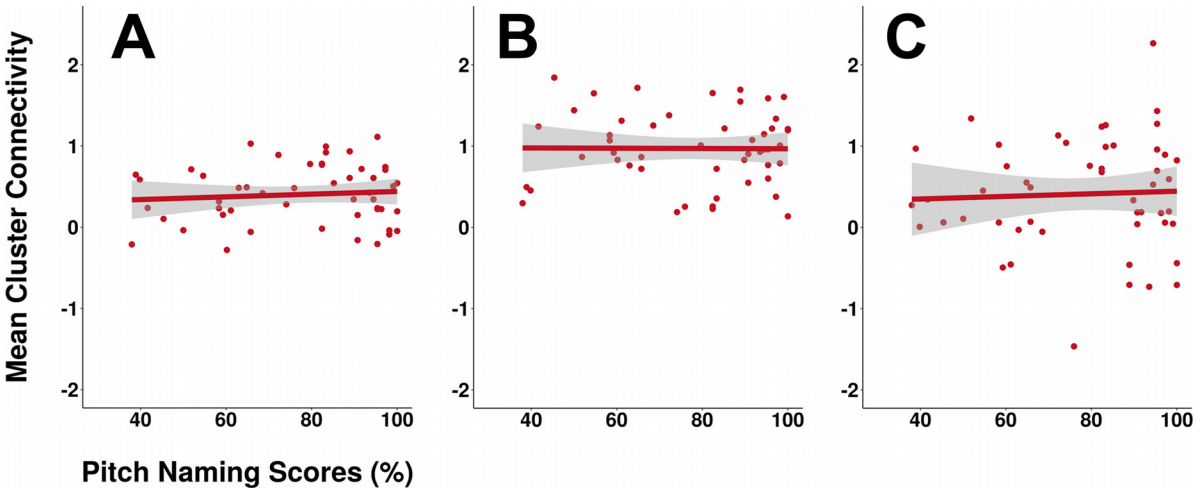
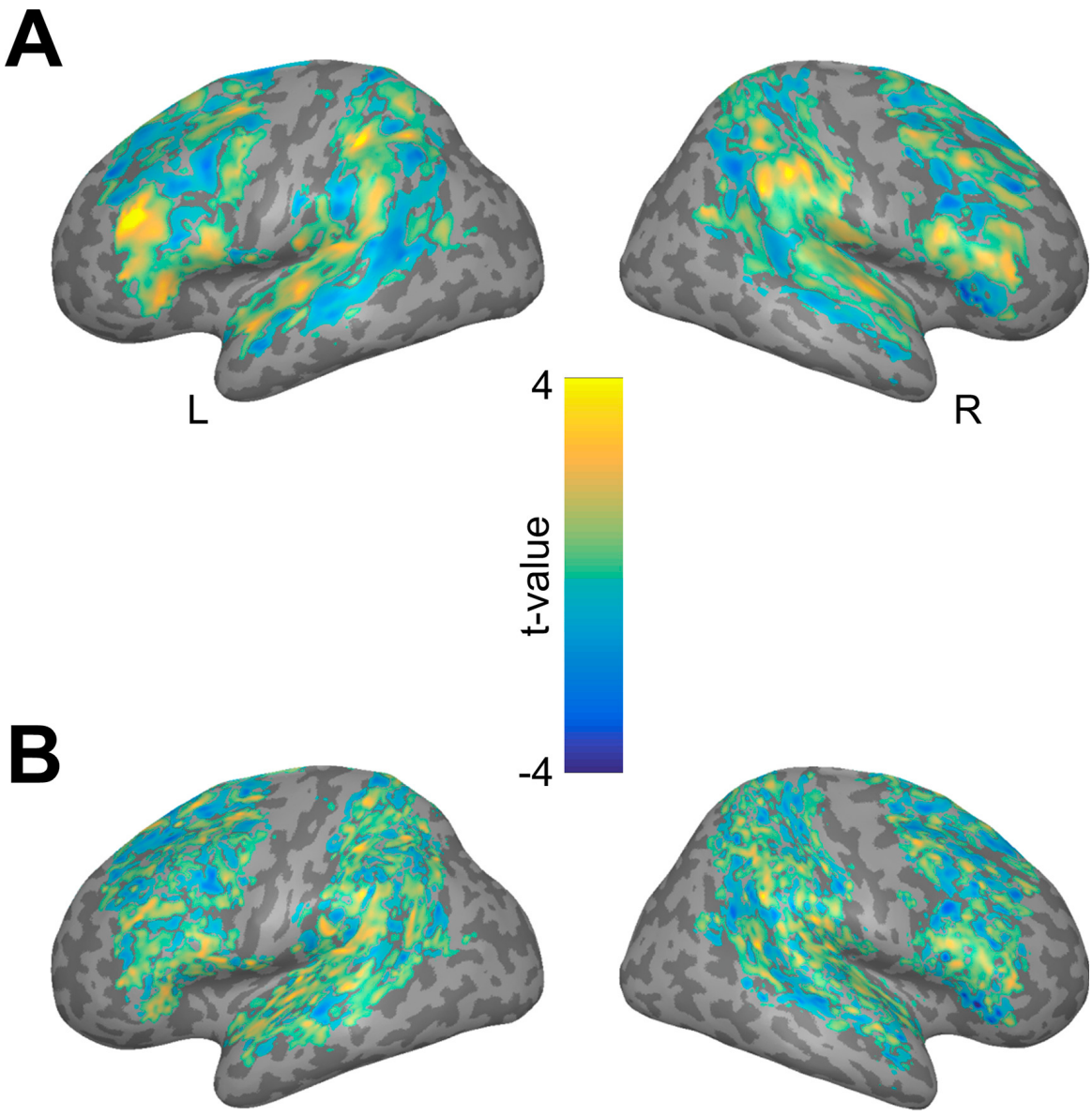
8 Supplementary Figures



Supplementary Figure 1 (Study II): Two-tailed Pearson correlations between mean connectivity in significant clusters of the mass univariate analysis and Pitch-naming scores of AP musicians. (A) Local connectivity within the left middle frontal gyrus (MFG) (r = 0.090, P = 0.269); (B) Local connectivity within the left intraparietal sulcus (IPS) (r = −0.007, P = 0.519); (C) Global connectivity within the right superior parietal lobule (SPL) (r = 0.045, P = 0.378). Gray areas denote the 95% confidence intervals.



Supplementary Figure 2 (Study II): Descriptive uncorrected mass-univariate statistics of local connectivity calculated from smoothed (A) and unsmoothed (B) fMRI data. Green and yellow colors display brain areas with higher mean local connectivity in AP musicians relative to Non-AP musicians. Light blue and dark blue colors display brain areas with higher mean local connectivity in Non-AP musicians relative to AP musicians. T-value maps were reduced to AP-relevant areas of the auditory, prefrontal and parietal cortex.

9 Curriculum Vitae

Personal information

Christian Brauchli
Nationality: Swiss
Born October 25, 1988

Profile

PhD student, working as neuroscientist with data science relevant skills such as 1) the handling of large datasets using scripted pipelines 2) the application of univariate and multivariate analyses and 3) the interpretation and presentation of results.

Education

October 2015 – March 2019: PhD studies in Neuropsychology

University of Zurich, Division Neuropsychology

2010 - 2015: Bachelor and Master in Psychology, minor Biology

University of Zurich

Acquired skills and achievements during the PhD studies

Programming languages

Proficient knowledge of R, SQL, MATLAB
Good knowledge of Python, Bash-Shell
Basic knowledge of Java, HTML

Office Software

Proficient knowledge of Excel, Word, PowerPoint, LibreOffice

Methods

Parametric und non-parametric statistics
Application of diverse machine learning algorithms (kNN, SVM, Random Forest)
Electroencephalography and magnetic resonance imaging

Presentations, teaching and supervision

Presentation at the Neuromusic VI conference, Harvard Medical school
Internal presentations
Lecturer in master seminars
Supervision of a master thesis, supervision of interns

Publications

Brauchli, C., Elmer, S., Rogenmoser, L., Burkhard, A., & Jäncke, L. (2018). Top-down signal transmission and global hyperconnectivity in auditory-visual synesthesia: Evidence from a functional EEG resting-state study. *Human Brain Mapping*, 39(1), 522–531.

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